Innovation Will Eliminate the Need for Inhalation Anesthesia

Steven L. Shafer, M.D.
Professor of Anesthesiology, Perioperative and Pain Medicine, Stanford University
Adjunct Associate Professor of Biopharmaceutical Sciences, UCSF
Editor-in-Chief, Anesthesia & Analgesia

Disclosures

- Signature Therapeutics (PF0713)
- Medicines Company (ABP-700)
- Johnson & Johnson
  - S-ketamine for psychiatric use
  - Sedasys
- Branequest
- Fresenius-Kabi
- FDA SGE

Disclosures

- AstraZeneca
- Novartis
- Takeda
- Grunenthal
- Concentric Analgesics
- Singchn
- Alexza

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No, it won’t.

I concede the debate.

Intravenous “anesthetic” drugs

- Hypnotics
  - Propofol, midazolam, etomidate, dexmedetomidine, ketamine
- Analgesics
  - Fentanyl, remifentanil, hydromorphone
  - Ketorolac, acetaminophen, diclofenac
- Relaxants
  - Rocuronium, vecuronium, cisatracurium

INNOVATIONS!

- Hypnotics
  - Propofol, midazolam, etomidate, dexmedetomidine, ketamine
- Analgesics
  - Fentanyl, remifentanil, hydromorphone
  - Ketorolac, acetaminophen, diclofenac
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  - Rocuronium, vecuronium, cisatracurium

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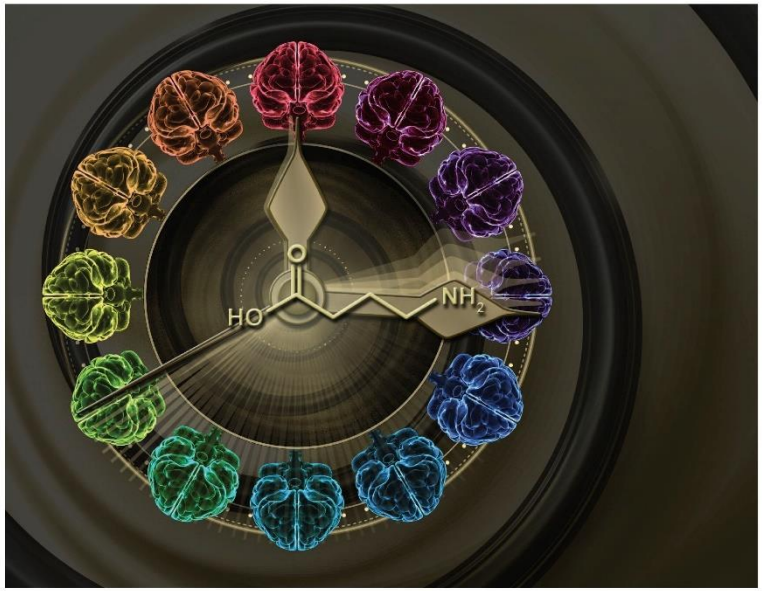

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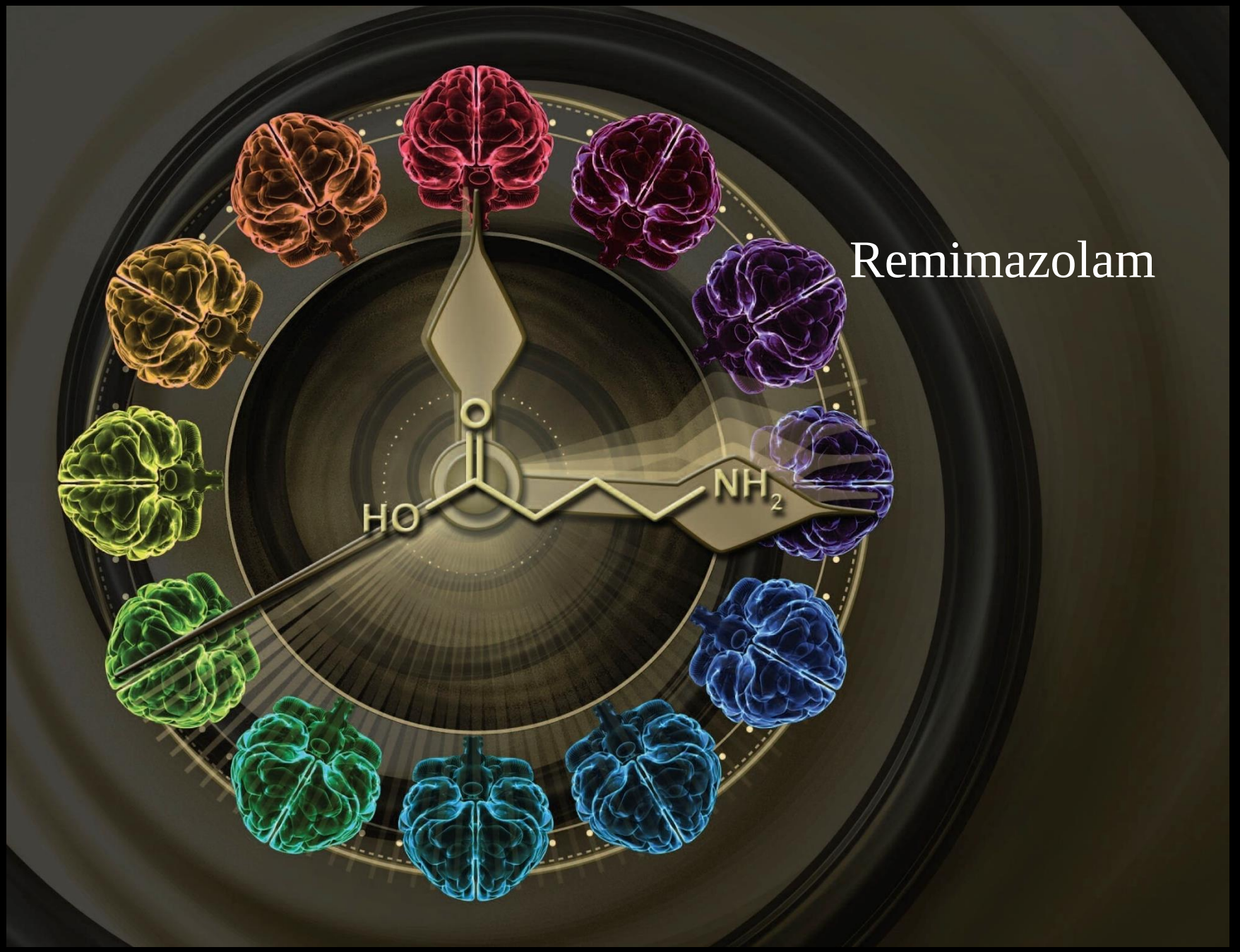
HO
NH2


Remimazolam
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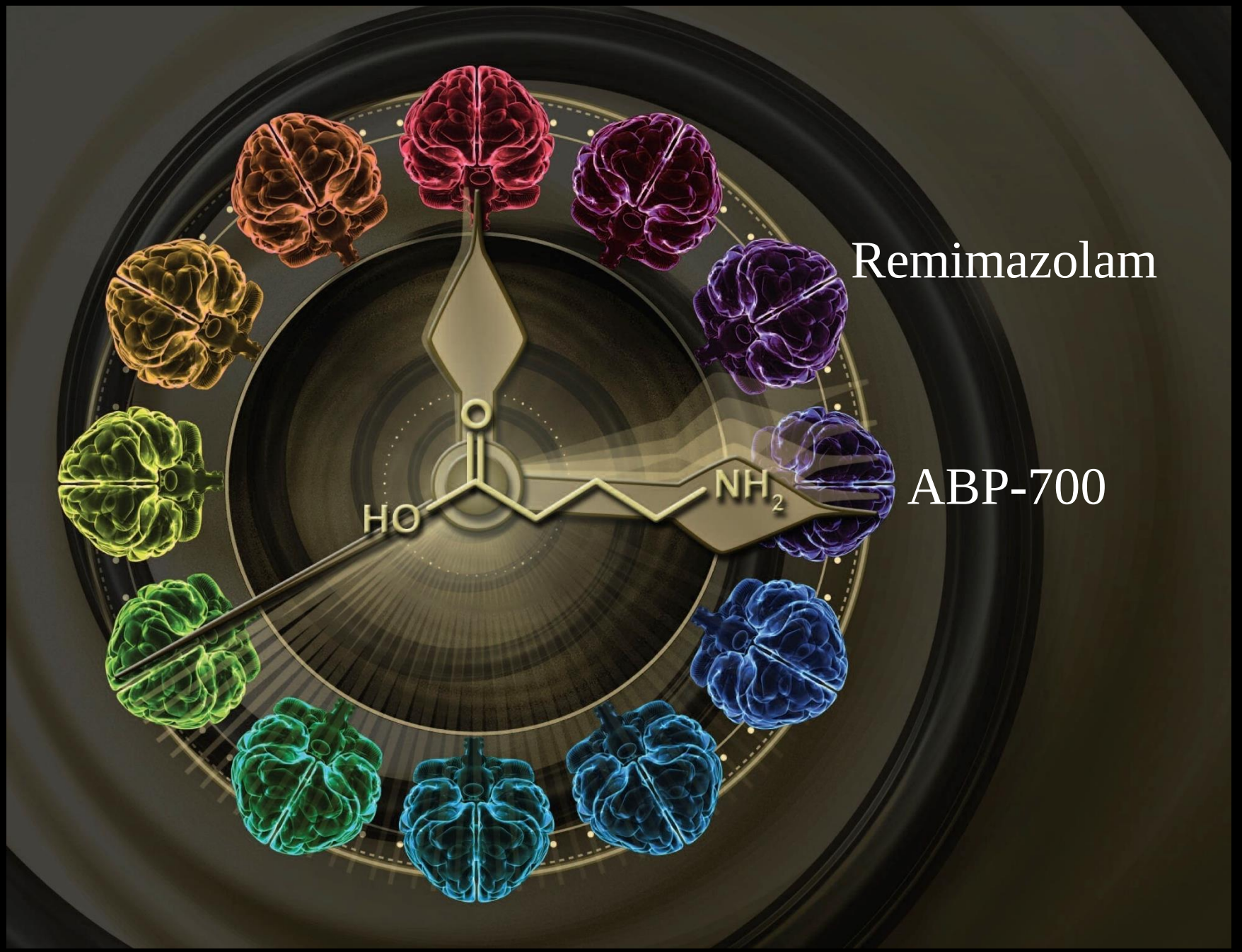
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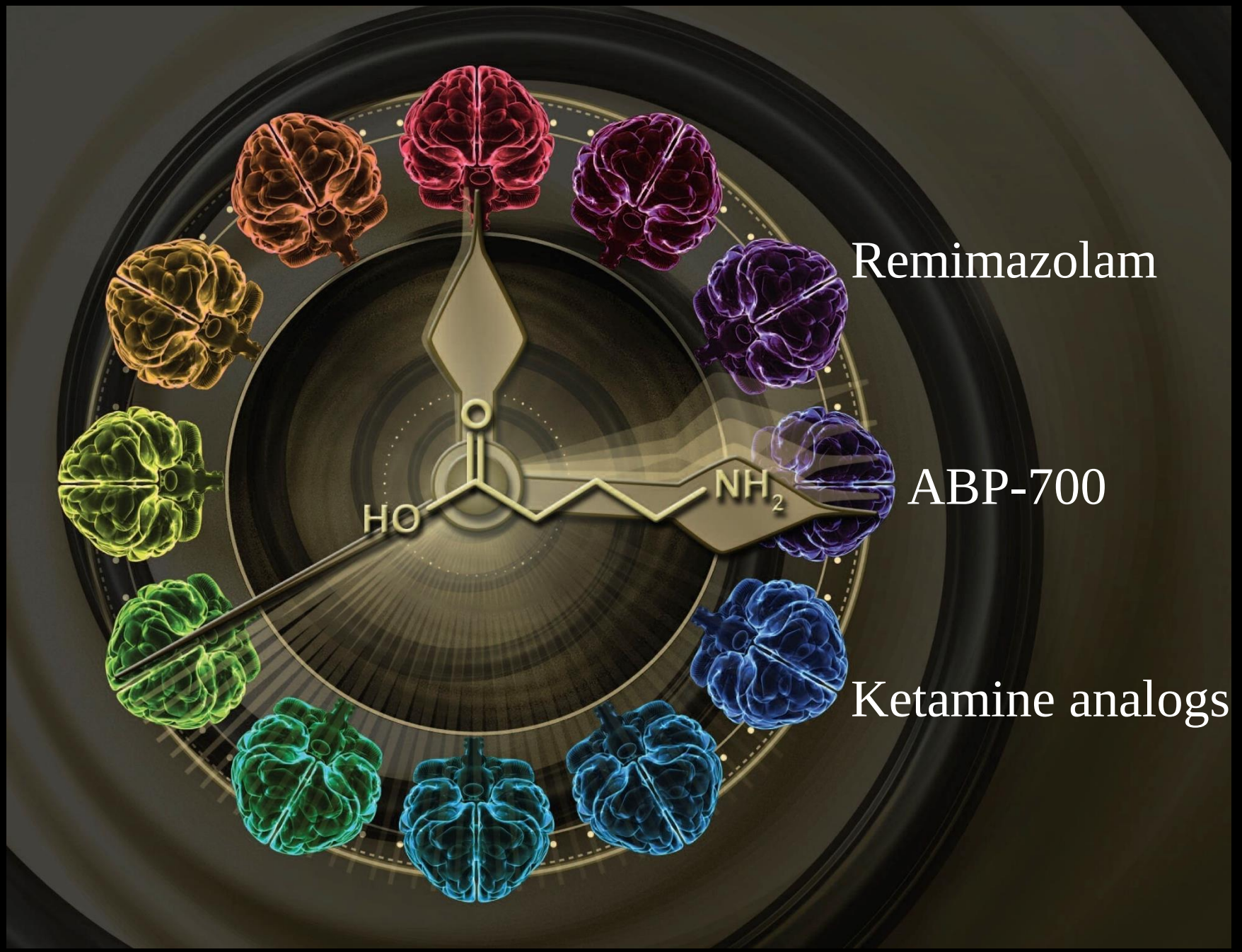

Remimazolam
ABP-700
Ketamine analogs
HO
NH2

Society for Technology in Anesthesia

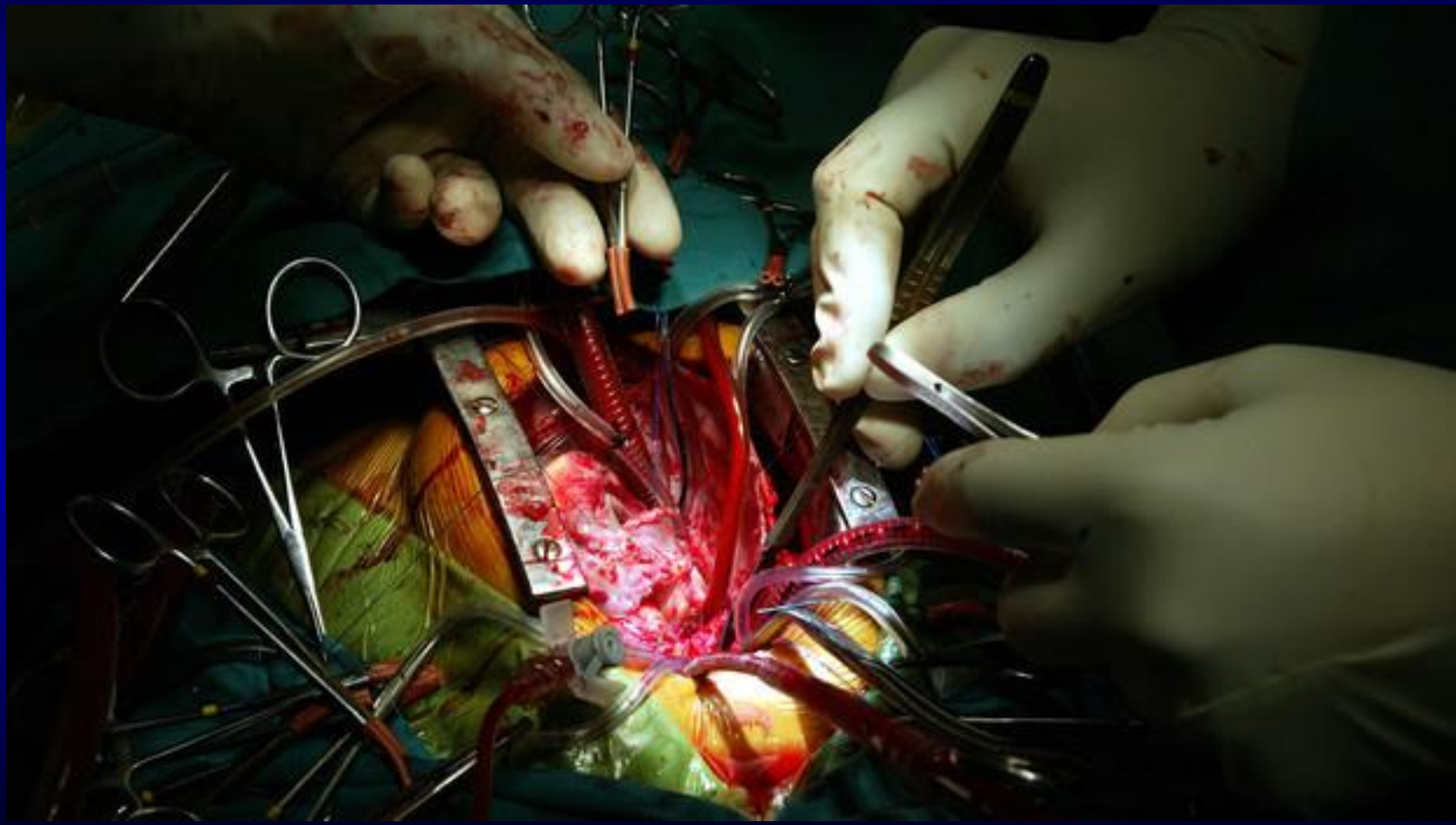
2016 Annual Meeting

The Future of Anesthesiology and Innovation in Perioperative Care

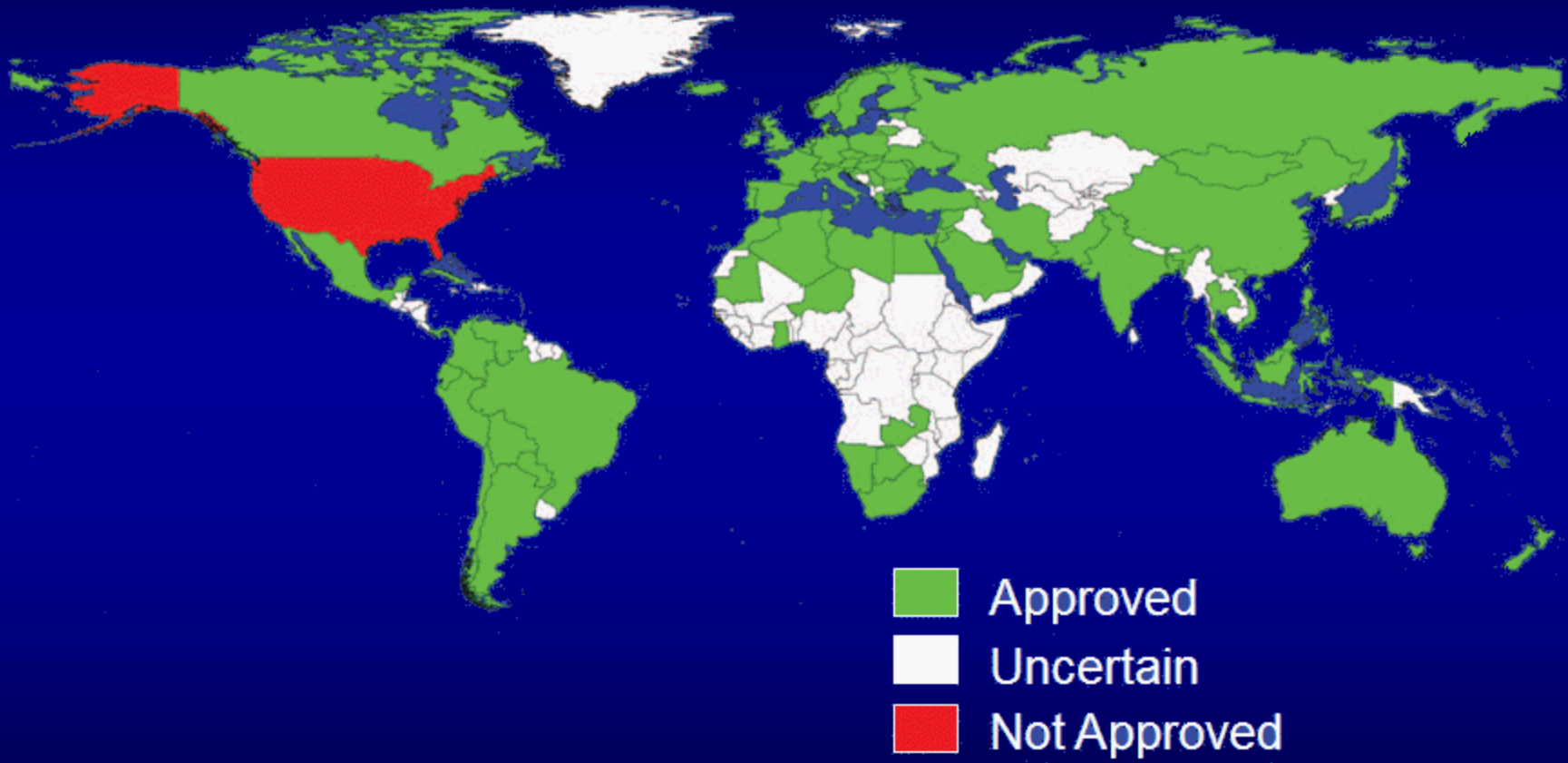
What technology can replace inhaled anesthetics for …

Children?

Cardiac Surgery?



Americans?



Global Status of Target Controlled Infusions of Anesthetics

The Future of Anesthesiology and Innovation in Perioperative Care

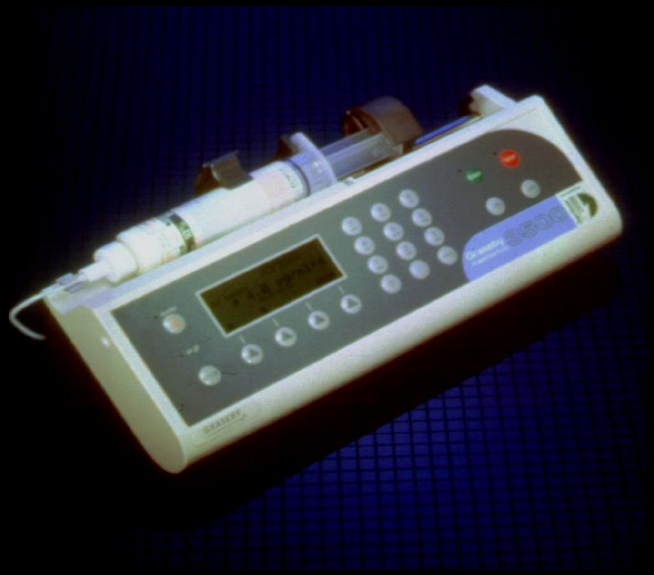
No innovation in intravenous anesthetic delivery has reached the United States for 30 years

The Future of Anesthesiology and Innovation in Perioperative Care

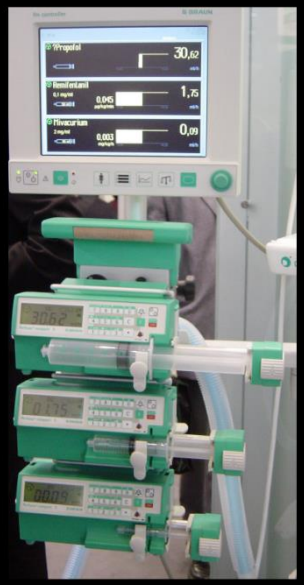
The Past of Anesthesiology and Innovation in Perioperative Care

Target Controlled Infusions

1980s

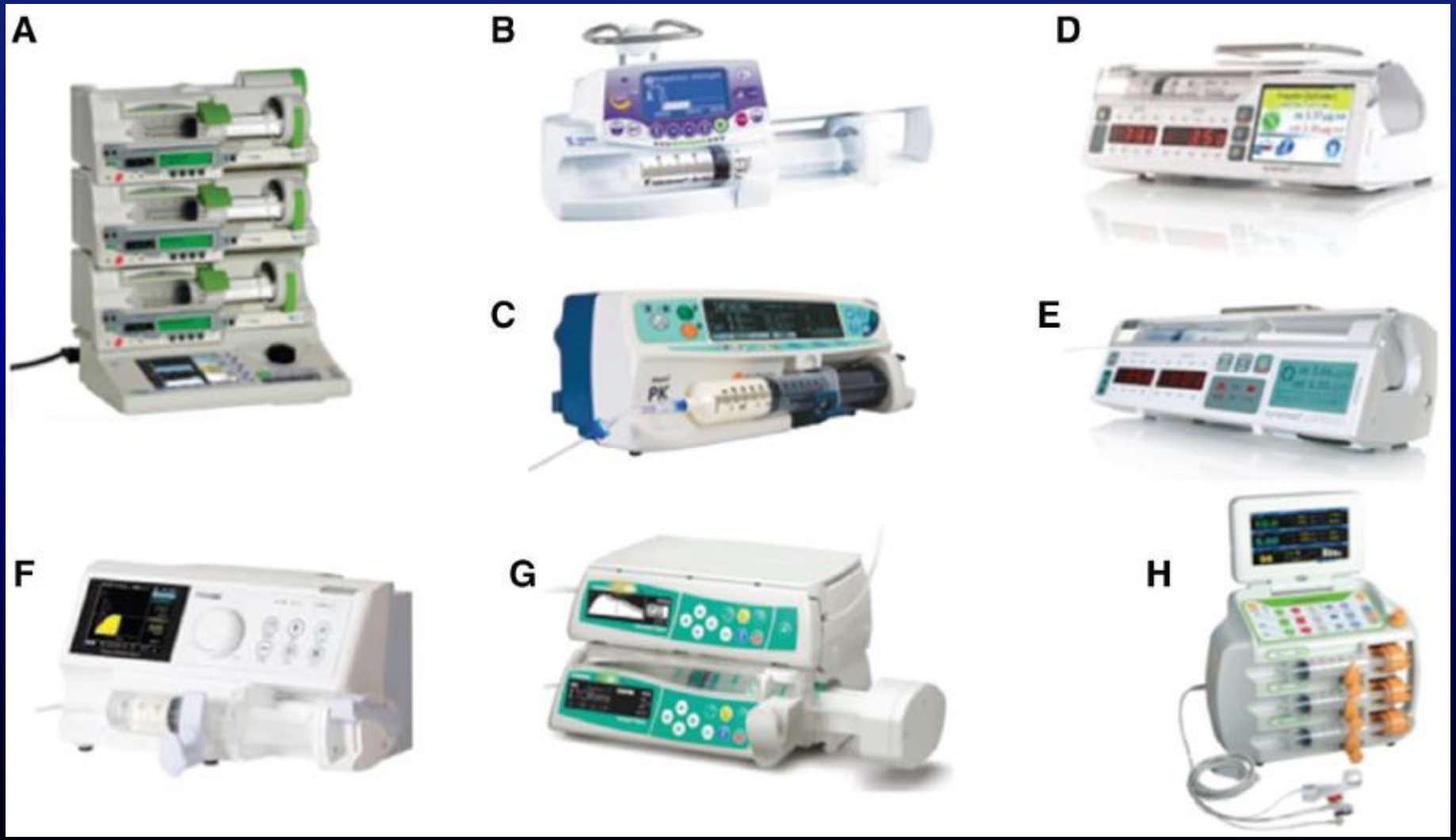


1990s



2000s

The Past of Anesthesiology and Innovation in Perioperative Care



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ANESTHESIA & ANALGESIA®

FEATURED ARTICLE COLLECTION
Target-Controlled Infusions

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Old-world puppet theater reflects just how antiquated it may seem in the face of current technology to be manually administering powerful anesthetic drugs to ill-defined endpoints. Against the backdrop evocative of the passage of time, our patient descends into sleep while a powerful figure, an overseer of her consciousness, inundates her with hypnotic elixir.

International Society for Anaesthetic Pharmacology

Preclinical Pharmacology Section Editor: Markus W. Hollmann

Anesthetic Clinical Pharmacology Section Editor: Ken B. Johnson

REVIEW ARTICLE

CME

The History of Target-Controlled Infusion

Michel M. R. F. Struys, MD, PhD, FRCA (Hon),*† Tom De Smet, PhD,‡
John (Iain) B. Glen, BVMS, PhD, FRCA,§ Hugo E. M. Vereecke, MD, PhD,*
Anthony R. Absalom, MBChB, FRCA, MD,* and Thomas W. Schnider, Prof Dr Med‖

Target-controlled infusion (TCI) is a technique of infusing IV drugs to achieve a user-defined predicted ("target") drug concentration in a specific body compartment or tissue of interest. In this review, we describe the pharmacokinetic principles of TCI, the development of TCI systems, and technical and regulatory issues addressed in prototype development. We also describe the launch of the current clinically available systems. (Anesth Analg 2016;122:56–69)

REVIEW ARTICLE

Target-Controlled Infusion: A Mature Technology

Anthony R. Absalom, MBChB, FRCA, MD,* John (Iain) B. Glen, BVMS, PhD, FRCA,† Gerrit J. C. Zwart, MD,* Thomas W. Schnider, MD, PhD,‡§ and Michel M. R. F. Struys, MD, PhD, FRCA (Hons)*‖

Target-controlled infusions (TCIs) have been used in research and clinical practice for >2 decades. Nonapproved TCI software systems have been used during the conduct of almost 600 peer-reviewed published studies involving large numbers of patients. The first-generation pumps were first approved in 1996, and since then an estimated 25,000 units have been sold and used. Second-generation pumps were first approved in 2003. During 2004 to 2013, >36,000 units were sold. Currently, TCI systems are approved or available in at least 96 countries. TCI systems are used to administer propofol and opioids for IV sedation and general anesthesia for millions of patients every year. In countries where TCI systems are approved, nonapproved software is still commonly used in studies of the pharmacology of hypnotics and opioids, because research software offers greater flexibility than approved TCI systems. Research software is also readily integrated into data management modules. Although TCI is a part of established practice around the world, TCI devices have not received regulatory approval in the United States. In the United States, TCI administration of propofol and opioids for sedation and anesthesia is only possible using research software in IRB-approved research studies. (Anesth Analg 2016;122:70–8)

REVIEW ARTICLE

The Safety of Target-Controlled Infusions

Thomas W. Schnider, Prof. Dr. med.,*† Charles F. Minto, MBChB, PhD, FANZCA,‡
Michel M. R. F. Struys, MD, PhD, FRCA (Hon),§‖
and Anthony R. Absalom, MBChB, FRCA, MD (UCT)§

Target-controlled infusion (TCI) technology has been available in most countries worldwide for clinical use in anesthesia for approximately 2 decades. This infusion mode uses pharmacokinetic models to calculate infusion rates necessary to reach and maintain the desired drug concentration. TCI is computationally more complex than traditional modes of drug administration. The primary difference between TCI and conventional infusions is that TCI decreases the infusion rate at regular intervals to account for the uptake of drug into saturable compartments. Although the calculated infusion rates are consistent with manually controlled infusion rates, there are concerns that TCI administration of IV anesthetics could introduce unique safety concerns. After approximately 2 decades of clinical use, it is appropriate to assess the safety of TCI. Our aim in this article was to describe safety-relevant issues related to TCI, which should have emerged after its use in millions of patients. We collected information from published medical literature, TCI manufacturers, and publicly available governmental Web sites to find evidence of safety issues with the clinical use of TCI. Although many case reports emphasize that IV anesthesia is technically more demanding than inhaled anesthesia, including human errors associated with setting up IV infusions, no data suggest that a TCI mode of drug delivery introduces unique safety issues other than selecting the wrong pharmacokinetic model. This is analogous to the risk of selecting the wrong drug with current infusion pumps. We found no evidence that TCI is not at least as safe as anesthetic administration using constant rate infusions. (Anesth Analg 2016;122:79–85)

REVIEW ARTICLE

The Safety of Target-Controlled Infusions

THE OPEN MIND

Target-Controlled Infusions Could Improve the Safety and Efficacy of Emergency Department Propofol Sedation

Steven M. Green, MD,* and Baruch S. Krauss, MD, EdM†‡

Target-controlled infusion (TCI) technology is now well established worldwide, except in the United States where it has not been approved by the Food and Drug Administration. TCI provides clinicians the convenience of thinking in terms of target concentrations rather than bolus doses and infusion rates.[1] Target-controlled drug delivery is based on ever-advancing pharmacokinetic models,[2] enhancing accurate drug delivery, and decreasing variability relative to bolus injection dosing.[1]

in children. For the same reason, anesthesiologists choose to sedate with propofol, in our practice propofol is our principal deep sedative, with presedation analgesia achieved with titrated opioids.[7–10]

Current monitoring modalities detect but do not predict adverse events during procedural sedation. Therefore, there is no objective means to gauge the ongoing risk of ventilatory compromise, making it difficult to know when the patient is at high risk for adverse events. It may be chal-

International Society for Anaesthetic Pharmacology

REVIEW ARTICLE

The Safety of Target-Controlled Infusions

THE OPEN MIND

SPECIAL ARTICLE

Target-Controlled Infusions: Paths to Approval

Paul E. Dryden, BS, MBA

Target-controlled infusion of IV anesthetic drugs is approved worldwide with the exception of the United States. The purpose of this special article is to review regulatory pathways that could lead to target-controlled infusion (TCI) clearance or approval in the United States. (Anesth Analg 2016;122:86–9)

Medical devices are defined by the U.S. Food and Drug Administration (FDA) in section 201(h) of the Federal Food Drug & Cosmetic Act. A device is:

- "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:
- recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treat-

WHAT ARE THE MAJOR REGULATORY PATHWAYS FO MEDICAL DEVICES WITHIN THE UNITED STATES?

All regulatory pathways require demonstrating that device is safe and effective for the intended use and that th potential benefits to patients justify the risks associated wi any medical device. The 3 regulatory pathways for medic devices are as follows:

1. Premarket notification (510(k))—based on substanti equivalence compared with existing legally markete devices, referred to as "predicates."
2. Premarket Approval—data are generated, whic demonstrate device safety and effectiveness
3. De novo—based on the low-to-moderate risk devic

REVIEW ARTICLE

The Safety of Target-Controlled Infusions

THE OPEN MIND

SPECIAL ARTICLE

EDITORIAL

Target-Controlled Infusions: Surfing USA Redux

Steven L. Shafer, MD,* and Talmage Egan, MD†

For 2 mellow guys, our 2003 editorial about target-controlled drug infusions (TCI) of anesthetic drugs in *Anesthesiology* was pretty harsh. The subtitle was barbed: *Surfing USA Not!*[1] We made the snarky observation that "exactly 0 of the estimated 13 million propofol anesthetics administered worldwide with TCI since the introduction of the Diprifusor™ (AstraZeneca, Gothenburg, Sweden) in Europe, Asia, the South Pacific, South America, and Africa have been performed in North America."[1] We placed the blame for the fact that TCI was only unavailable in the United States directly on the Food and Drug Administration (FDA), who spent 8 years reviewing a TCI application from Graseby Medical (Graseby Medical Ltd., Upper Pemberton,

[Fresenius Kabi, Lake Zurich, IL]), not on the sa
pump. With propofol now at generic price points,
ness model has evaporated. That pump companies
submitted a TCI application to the FDA since prop
generic suggests that perhaps they do not see an
business proposition. Of course part of the calcu
the attractiveness of the TCI business proposition
the estimated cost of meeting the regulatory requ
so it is complicated.

In any case, we still do not have TCI in the Unit
However, commercialization of TCI has contin
where. Three articles in the current issue of *Ana*
Analgesia, solicited by the Editor-in-Chief (SLS) an

Target-Controlled Infusion: A Mature Technology

Anthony R. Absalom, MBChB, FRCA, MD,* John (Iain) B. Glen, BVMS, PhD, FRCA,† Gerrit J. C. Zwart, MD,* Thomas W. Schnider, MD, PhD,‡§ and Michel M. R. F. Struys, MD, PhD, FRCA (Hons)*‖

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Target-controlled infusion (TCI) systems have been in use for >2 decades. The history of the development of TCI and the underlying concepts is discussed in an accompanying article.[1]

Initially, only custom-made prototype systems were available, having been developed by different research groups who tended to use disparate names and acronyms to describe their systems. In 1996, a group of investigators proposed a standard nomenclature.[2] It included the use of the generic term original mode) or the effect site (e.g., the brain, based on the models of blood–brain equilibration) was introduced.

Since its introduction, TCI technology has transformed from a research tool in expert hands to a routine part of clinical anesthesia practice in many countries. However, the use of nonapproved software and prototypes did not stop with the introduction of commercial TCI systems. Several such programs also include data management modules that generate an electronic record of details indispensable for PK and pharmacody-

The World is Using TCI

- Over 500 peer-reviewed articles in Medline on TCI
- About 25K first generation systems sold through 2000.
- Most are now using second generation systems
  - Incorporate patient covariates
  - Target the effect site
  - About 35K second generation systems sold
- Conservative estimate of routine clinical use:
  - 20 million cases

The Safety of Target-Controlled Infusions

Thomas W. Schnider, Prof. Dr. med.,*† Charles F. Minto, MBChB, PhD, FANZCA,‡
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- Number of adverse events related to pharmacokinetic control in TCI:

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- Number of adverse events related to pharmacokinetic control in TCI:

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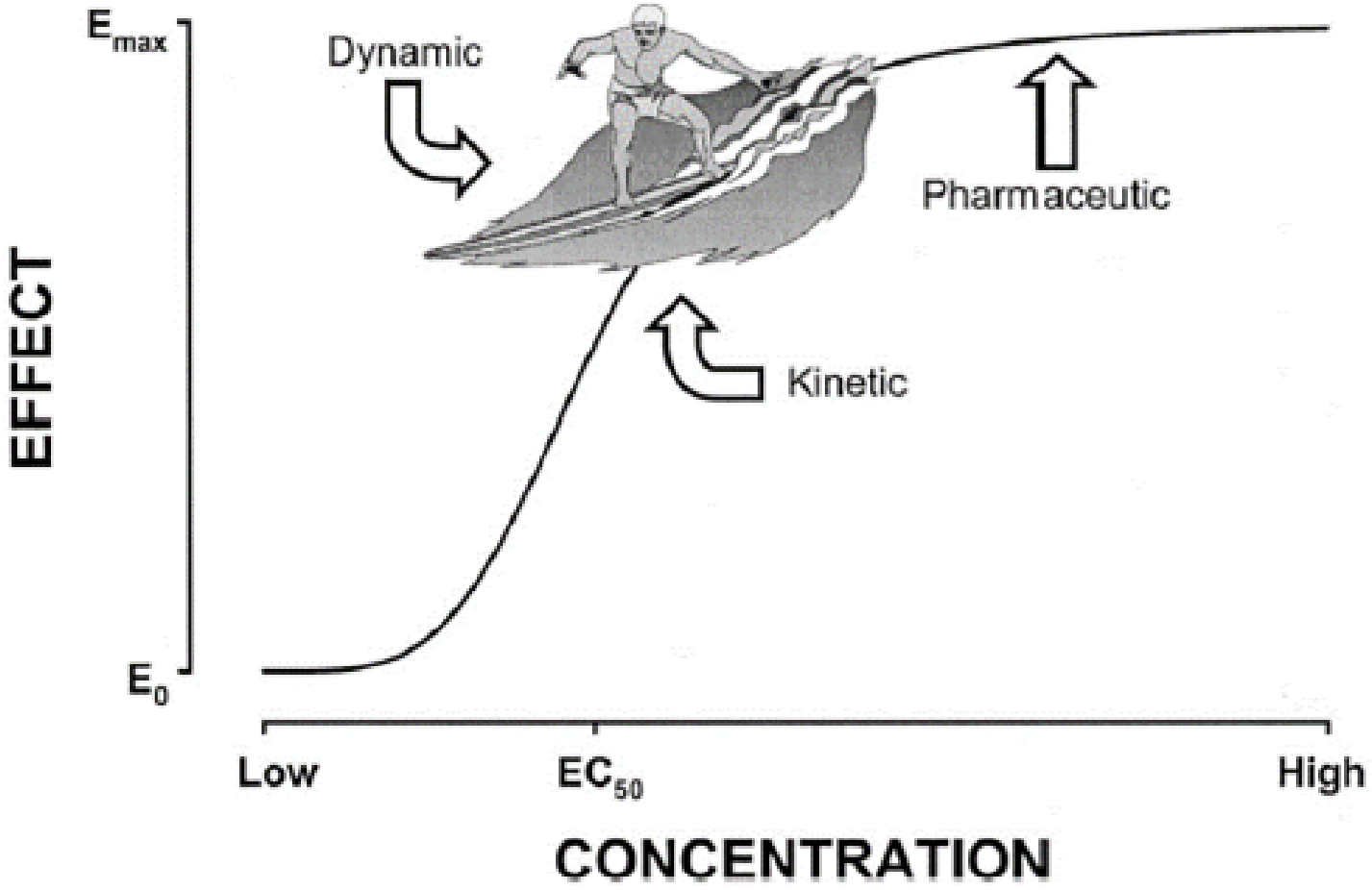
- "Not a single report has identified an adverse incident that was related to the TCI algorithm for a PK-based infusion."
- Conservative estimate: 20 million cases
- Rule of 3, upper 95% confidence estimate of risk is 1 in 7 million

Anesthesiology 2003; 99:1039–41

Target-controlled Infusions for Intravenous Anesthetics

Surfing USA Not!



Anesthesiology 2003; 99:1039–41

Target-controlled Infusions for Intravenous Anesthetics

Surfing USA Not!

Twenty years have elapsed since Helmut Schwilden first outlined the computer algorithm for anesthetic drugs. Although these developments began in Germany, American investigators added fundamental contributions. How ironic that America, the country that brought the world surfing,* continues to deny physicians access to the fundamental tools to surf the concentration response curves of intravenous anesthetic agents.

The Beach Boys, Surfin' USA, Capitol Records, Hollywood, 1963

Target-Controlled Infusions: Surfing USA Redux

Steven L. Shafer, MD,* and Talmage Egan, MD†

We have matured somewhat since 2003. We now have a better understanding of the statutory limitations that define exactly what the FDA can and cannot do. We recognize that no sponsor has attempted to bring TCI to the United States since 2003. The FDA obviously cannot approve devices for which an application has not been submitted.

Target-Controlled Infusions: Surfing USA Redux

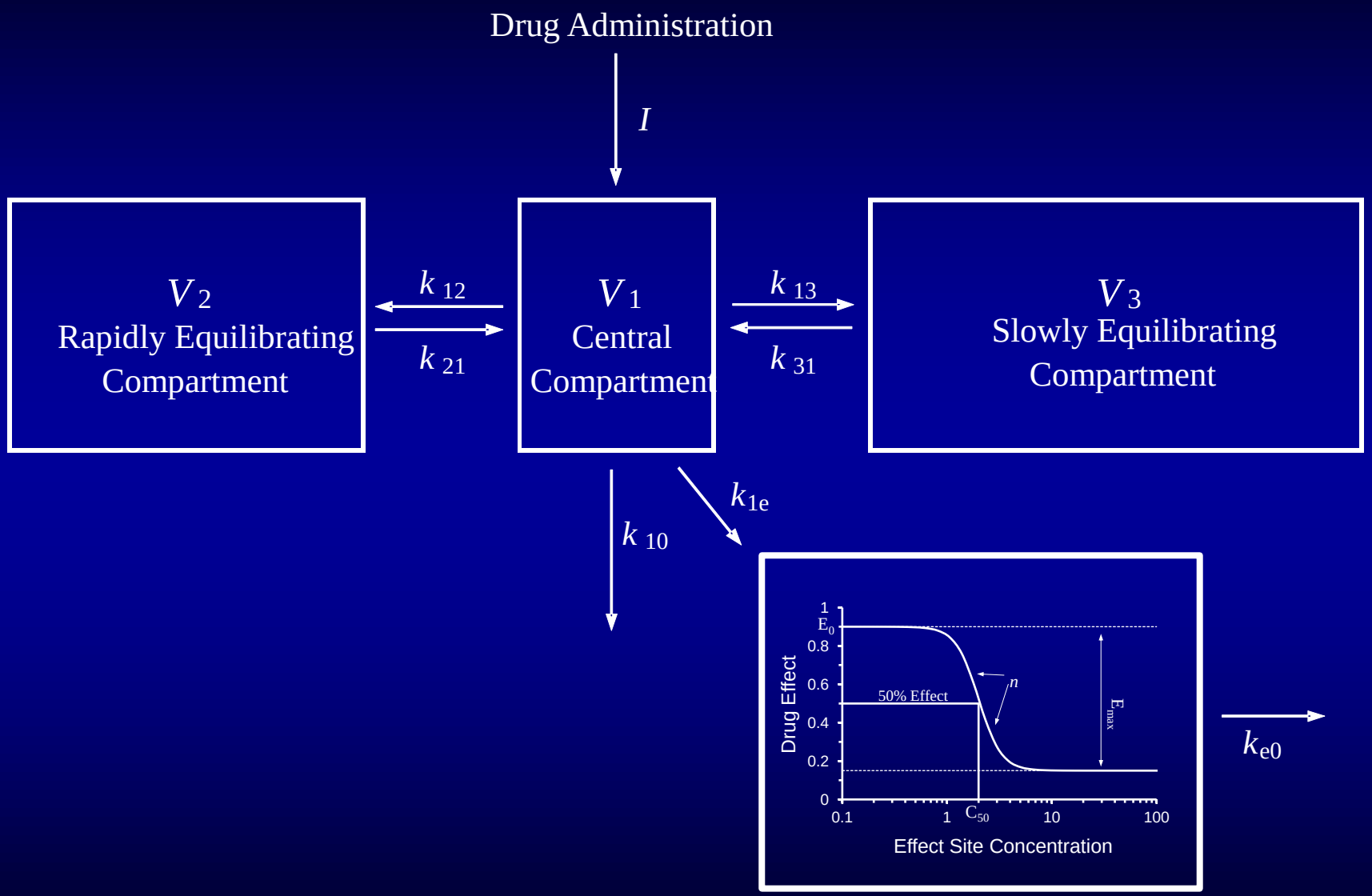
Steven L. Shafer, MD,* and Talmage Egan, MD†

For a given patient, a TCI device delivers a given infusion profile of drug within conventional limits of infusion accuracy.

Otherwise, it is just administering an ***approved*** drug, for an ***approved*** indication, at ***doses entirely consistent with the package insert***.

Why is TCI important for innovation in anesthetic drug delivery technology?

TCI is imbedded
in closed loop systems


Drug Administration
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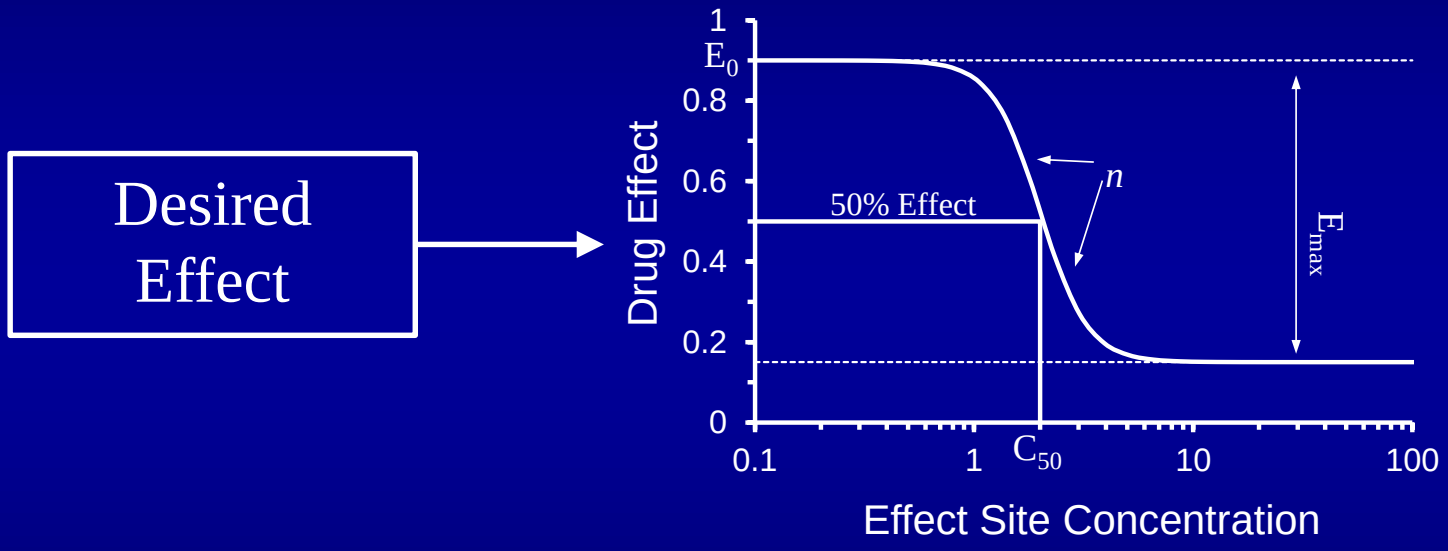
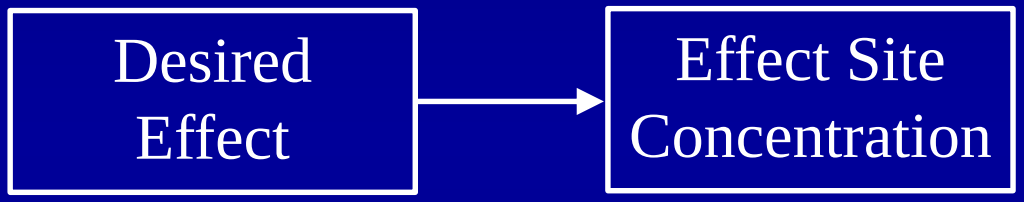
Model Based Controller

Model Based Controller



Model Based Controller



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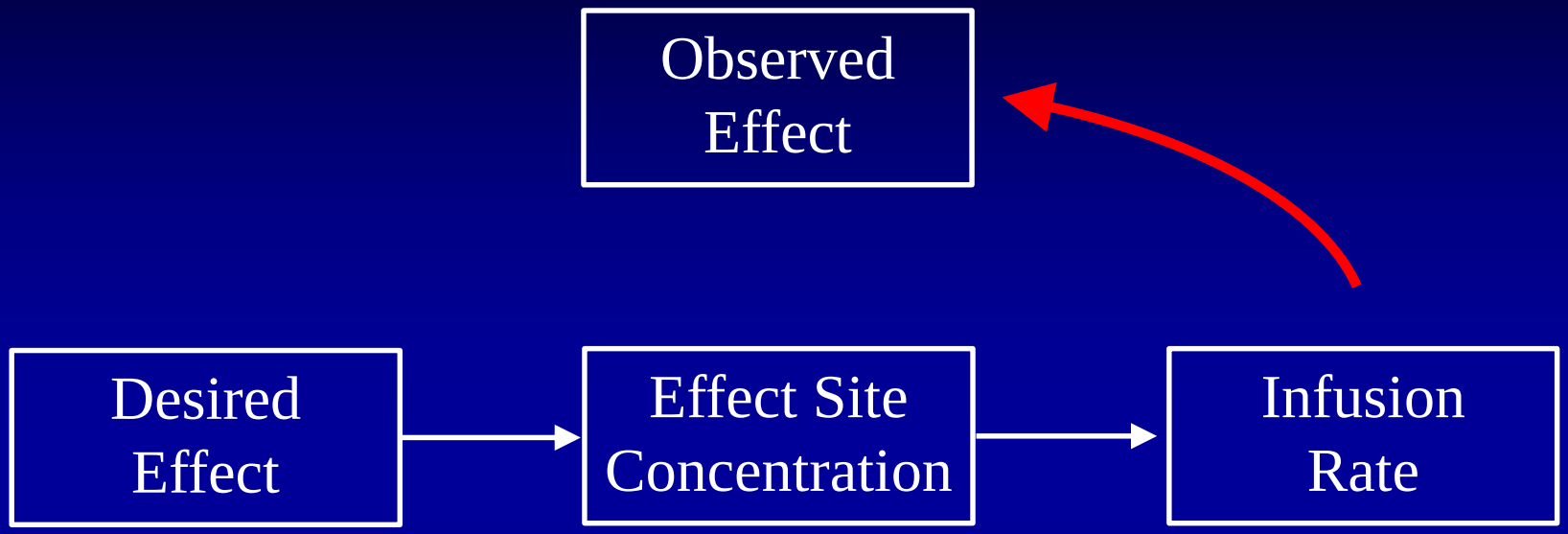

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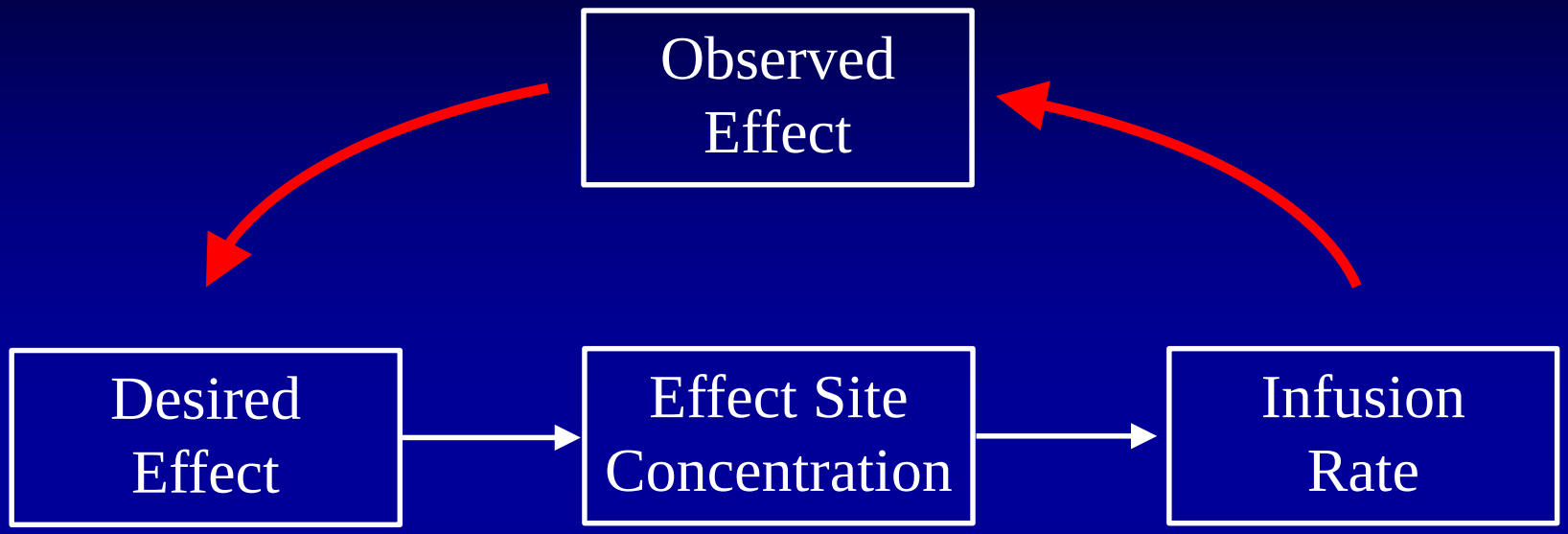

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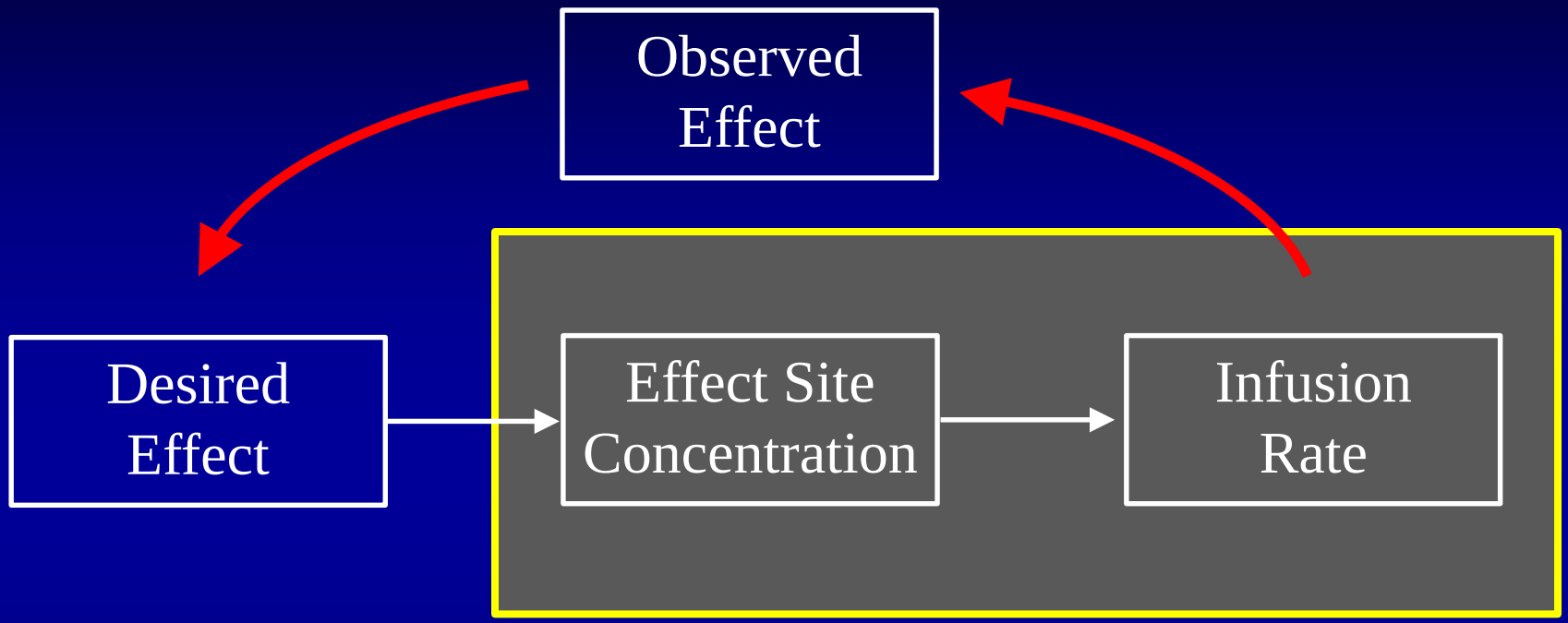


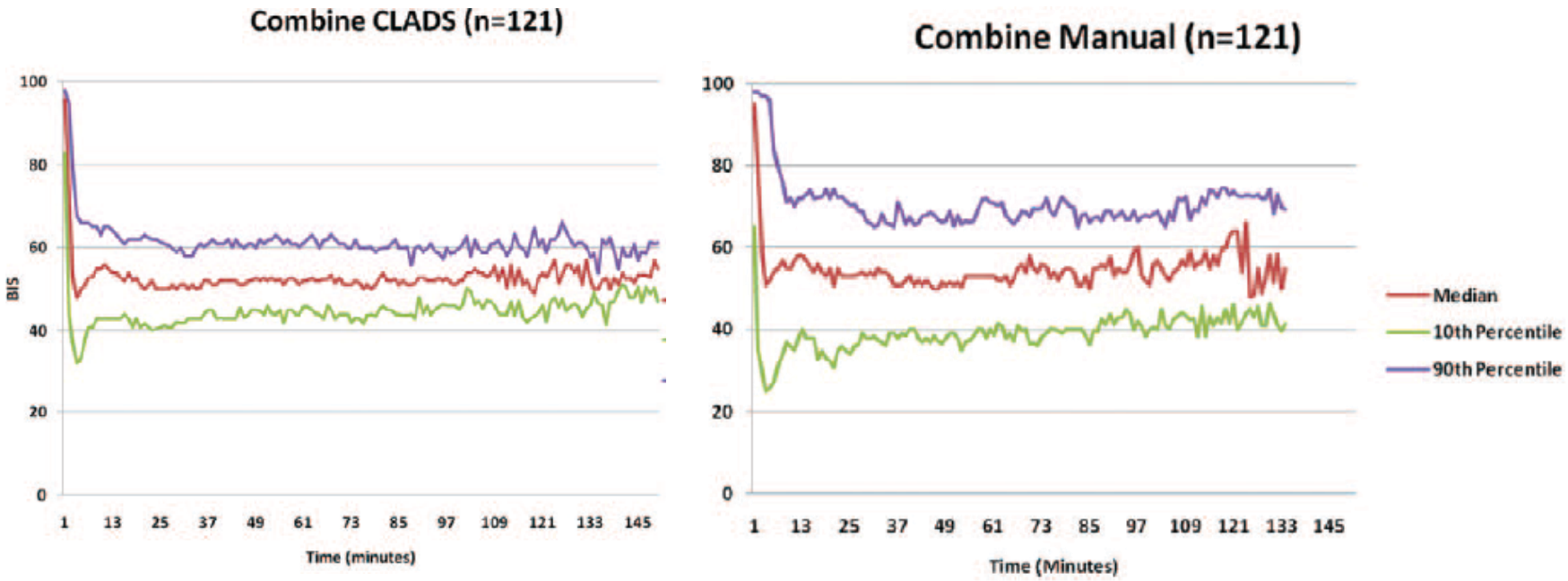
TCI

Society for Technology in Anesthesia

Section Editor: Maxime Cannesson

A Multicenter Evaluation of a Closed-Loop Anesthesia Delivery System: A Randomized Controlled Trial

Goverdhan D. Puri, MD, PhD,* Preethy J. Mathew, MD,* Indranil Biswas, MD,* Amitabh Dutta, MD,† Jayashree Sood, PGDHHM, FFARCS, MD, MBBS, FICA,† Satinder Gombar, MD,‡ Sanjeev Palta, MD,‡ Morup Tsering, MD,§ P. L. Gautam, MD,‖ Aveek Jayant, MD, DM,* Inderjeet Arora, MSc,* Vishal Bajaj, MD,¶ T. S. Punia, MD,¶ and Gurjit Singh, MSc#



%Time within target: 81 vs 61, $p < 0.0001$

Br. J. Anaesth. (1989), 62, 290-296

CLOSED-LOOP FEEDBACK CONTROL OF PROPOFOL ANAESTHESIA BY QUANTITATIVE EEG ANALYSIS IN HUMANS

H. SCHWILDEN, H. STOECKEL AND J. SCHUTTLER

If median EEG frequency was outside this range, the difference between the measured and predicted values served to adapt the model parameters. On the basis of the updated parameters, a new infusion scheme was calculated for achieving and maintaining a concentration inducing a median EEG frequency of 2.5 Hz.

Journal of Pharmacokinetics and Biopharmaceutics, Vol. 22, No. 6, 1994

Comparison of Some Control Strategies for Three-Compartment PK/PD Models

Chuanpu Hu, William S. Lovejoy, and Steven L. Shafer

This paper investigates several control strategies in the framework of a three-compartment PK model plus an effect site with a PD model. Using computer simulations under different assumptions, we show that a MAP (maximum *a posteriori*) Bayesian type of strategy is effective, nevertheless in high-risk situations a stochastic control strategy hedging against estimation errors provides better performance at computational cost.

Journal of Pharmacokinetics and Biopharmaceutics, Vol. 22, No. 6, 1994

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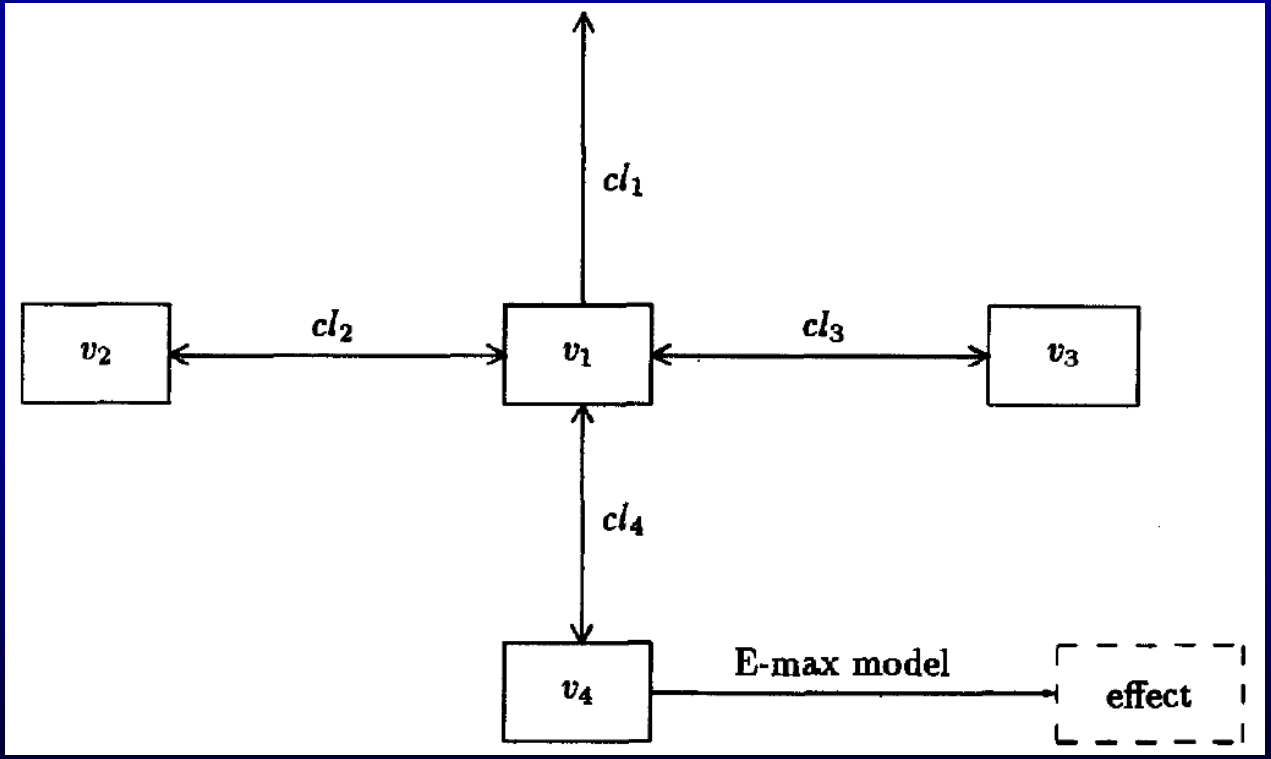
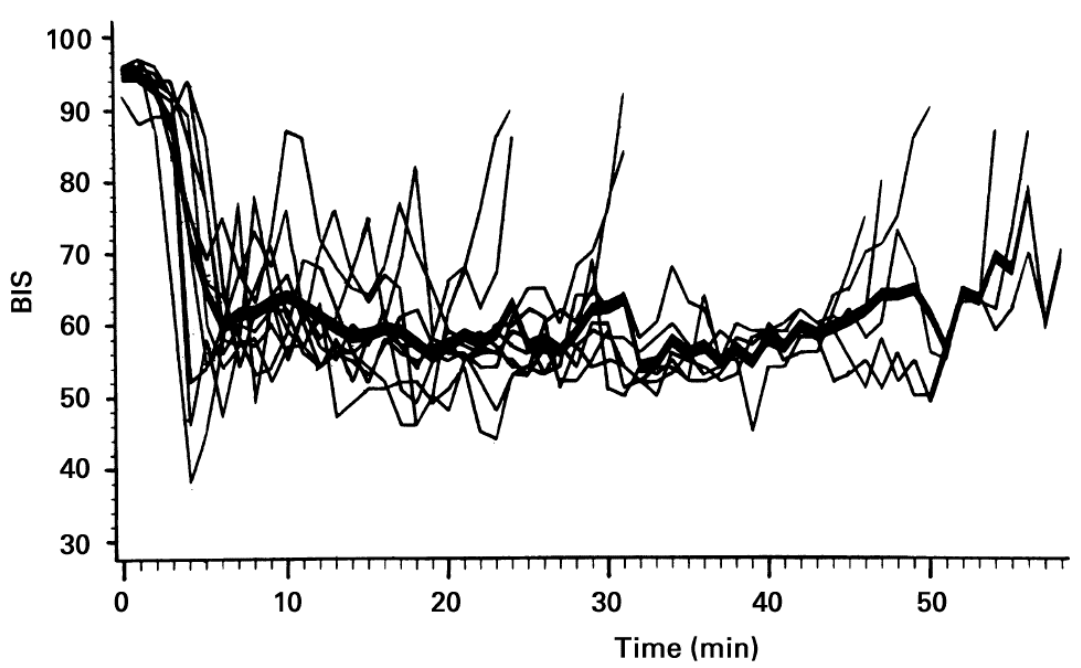


Anaesthesia, 1998, 53, pages 749–754

Closed-loop controlled administration of propofol using bispectral analysis

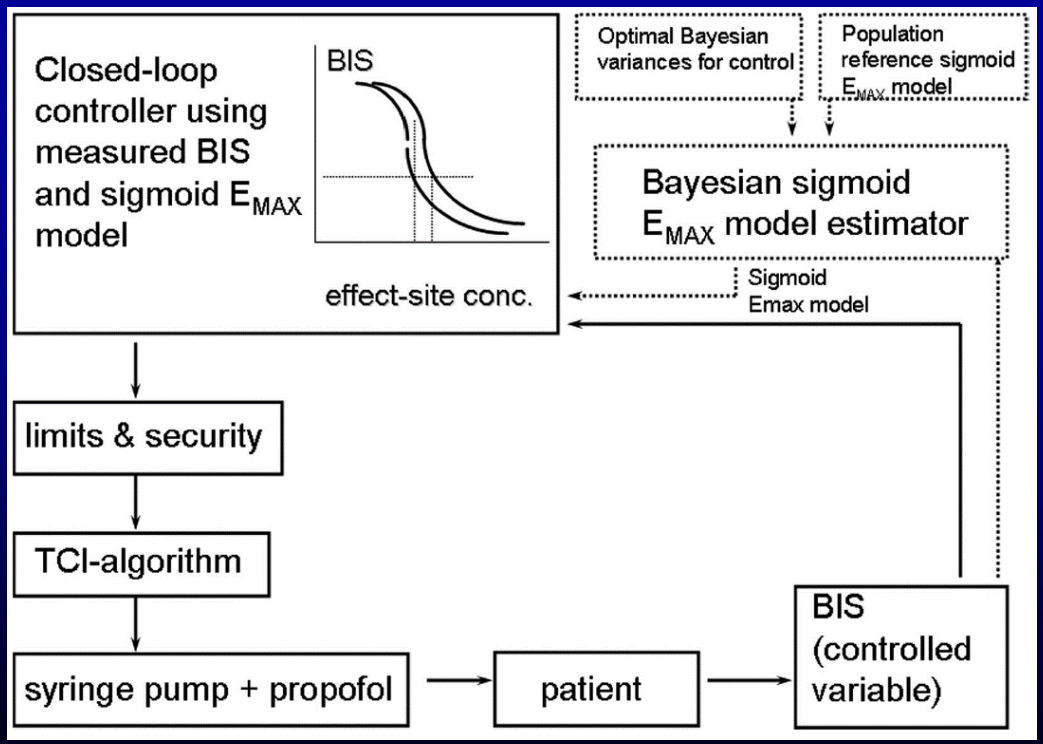
E. Mortier, M. Struys, T. De Smet, L. Versichelen and G. Rolly



Anesth Analg 2007;105:1629 –38

Estimation of Optimal Modeling Weights for a Bayesian-Based Closed-Loop System for Propofol Administration Using the Bispectral Index as a Controlled Variable: A Simulation Study

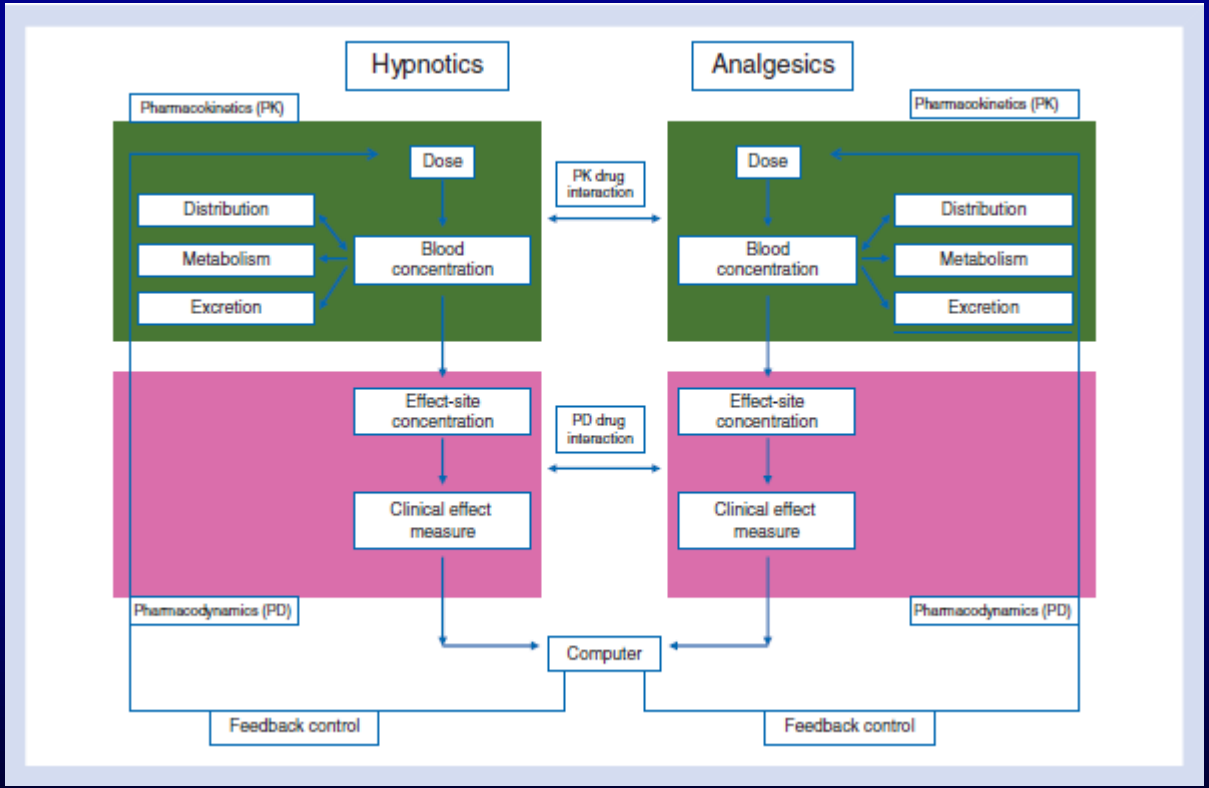
De Smet T, Struys MMRF, Greenwald S, Mortier EP, Shafer SL



British Journal of Anaesthesia 107 (1): 38–47 (2011)

Optimizing intravenous drug administration by applying pharmacokinetic/pharmacodynamic concepts

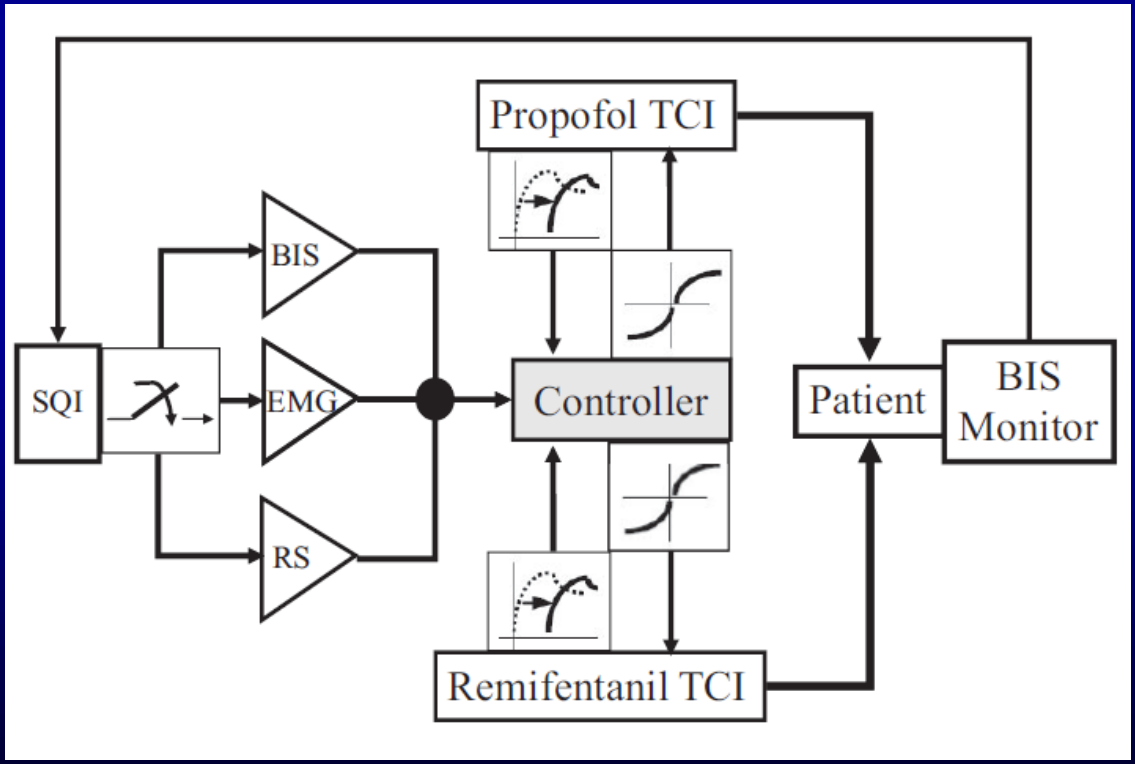
Struys, MMRF, Sahinovic M[1], Lichtenbelt BJ, Vereecke HEM, Absalom AR



Anesth Analg. 2011 Mar;112(3):546-57.

Closed-loop coadministration of propofol and remifentanil guided by bispectral index: a randomized multicenter study

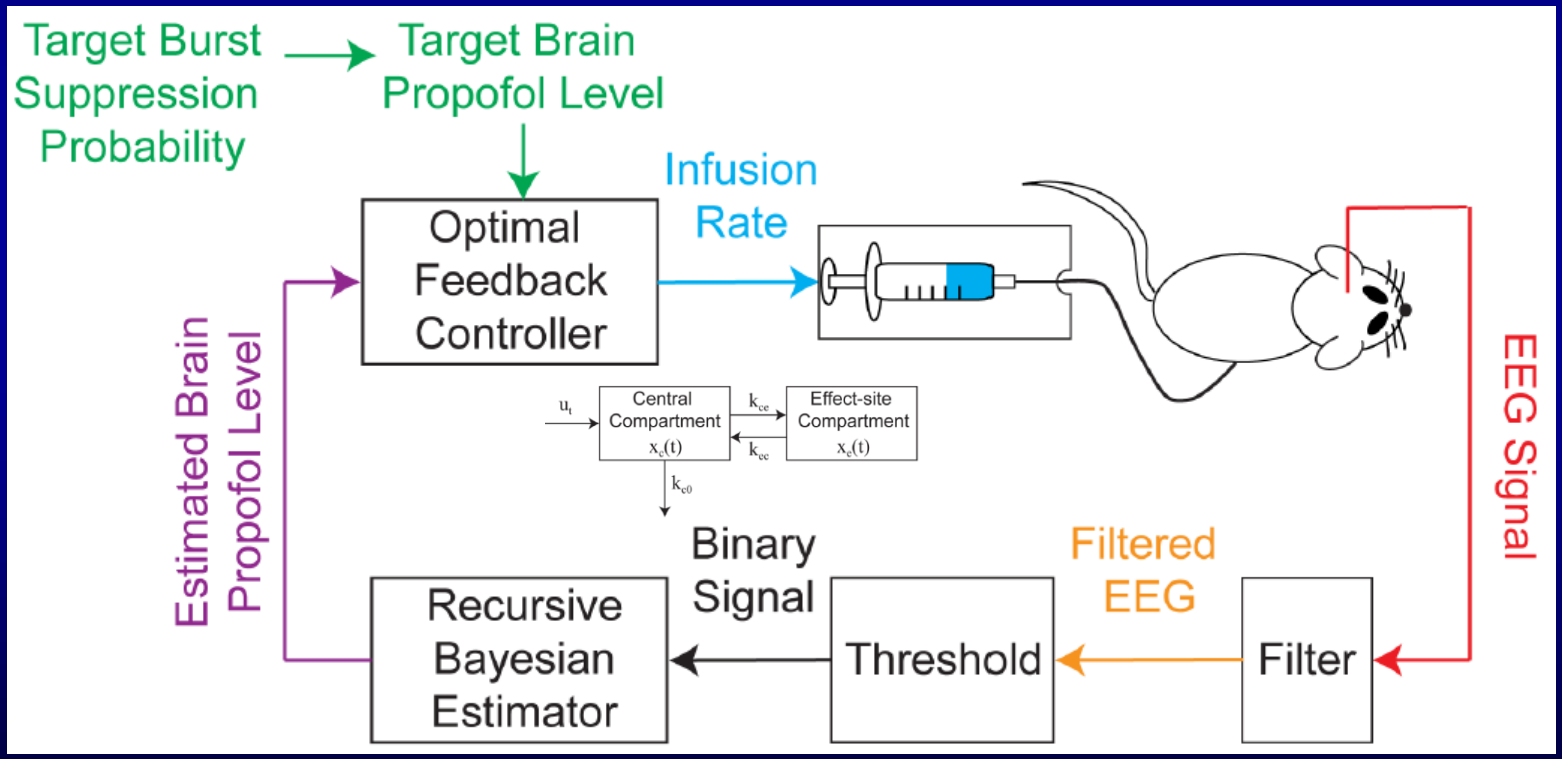
Liu N, Chazot T, Hamada S, Landais A, Boichut N, Dussaussoy C, Trillat B, Beydon L, Samain E, Sessler DI, Fischler M



PLOS Computational Biology 2013 9(10)

A Brain-Machine Interface for Control of Medically-Induced Coma

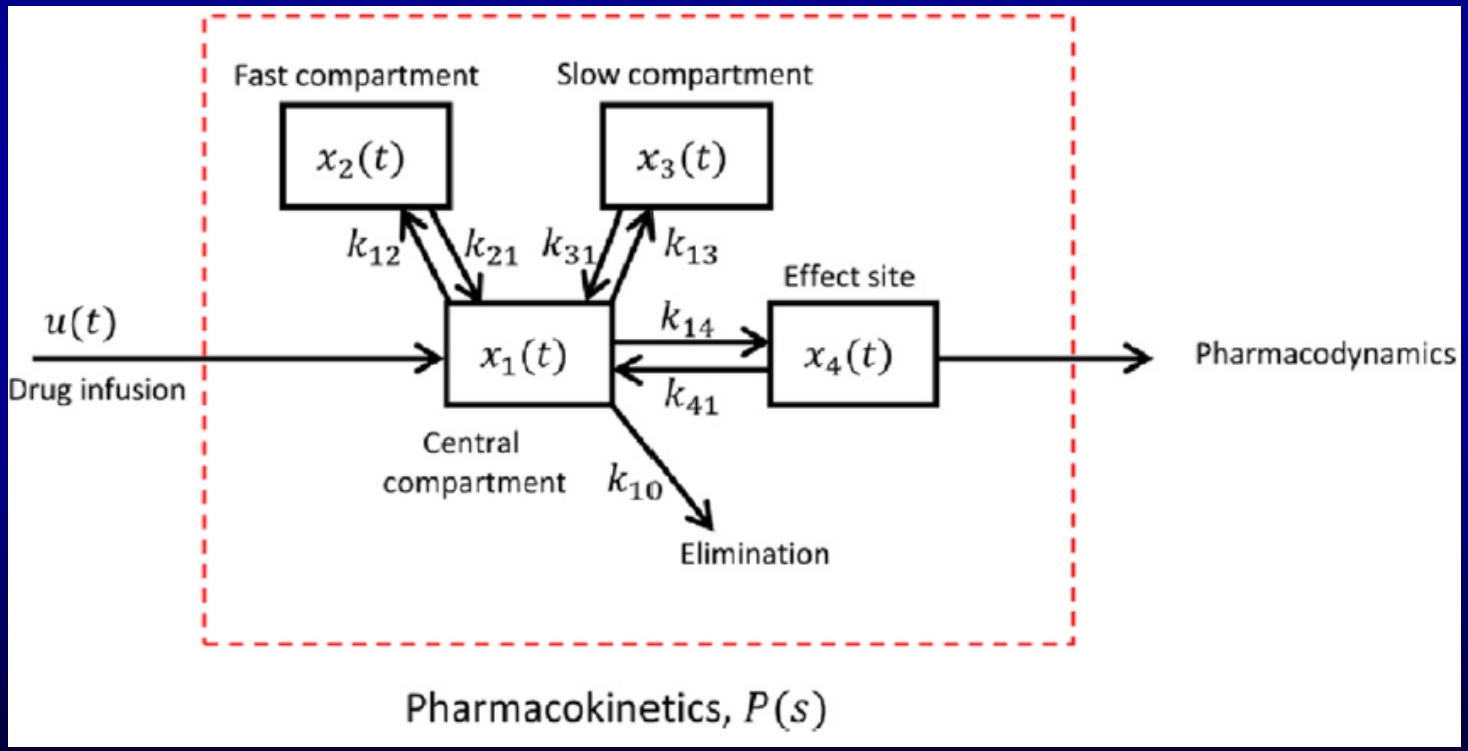
Shanechi MM, Chemali JJ, Liberman M, Solt K, Brown EN



J. Neural Eng. 12 (2015) 046004

Robust control of burst suppression for medical coma

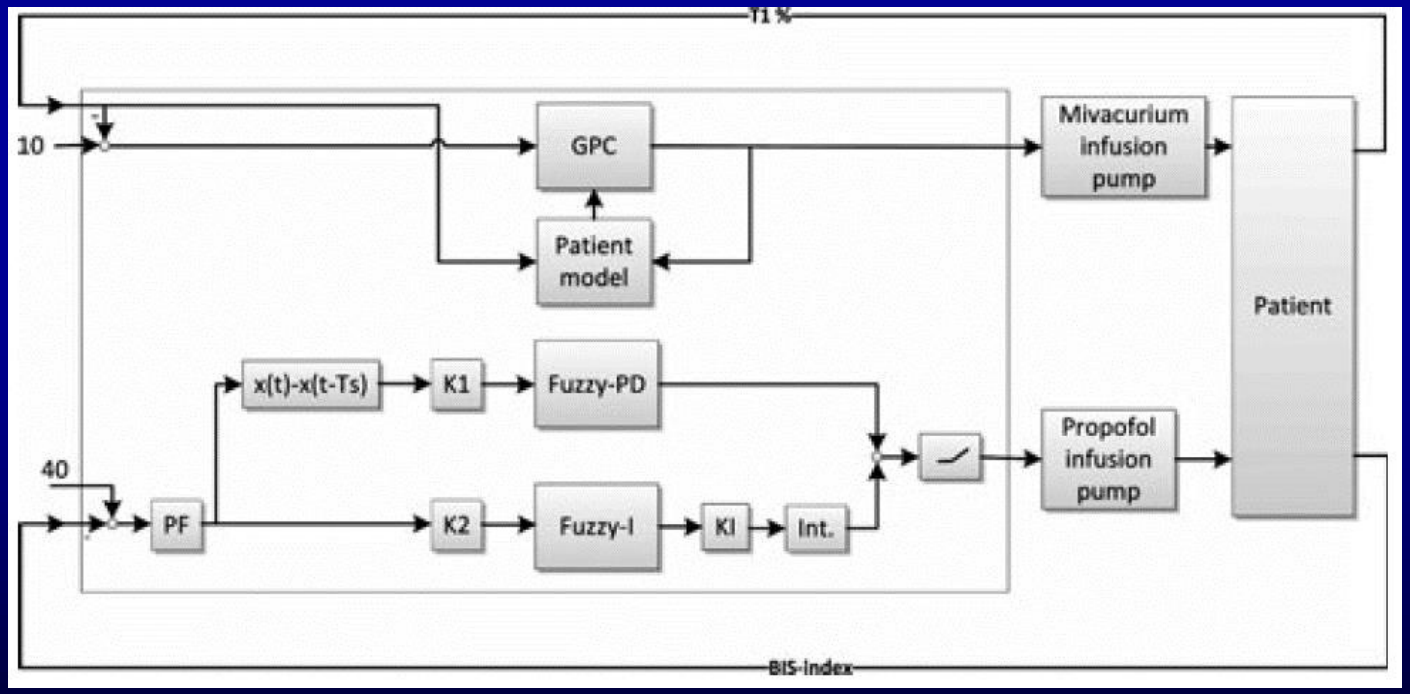
Westover MB, Kim ES, Ching SN, Patrick L Purdon PL, Brown EN



Anaesthesia, 2011, 66, pages 1112–1120

Clinical evaluation of a simultaneous closed-loop anaesthesia control system for depth of anaesthesia and neuromuscular blockade

Janda M, Simanski P. Bajorat J, Pohl B, Noeldge-Schomburg GFE, Hofmockel R



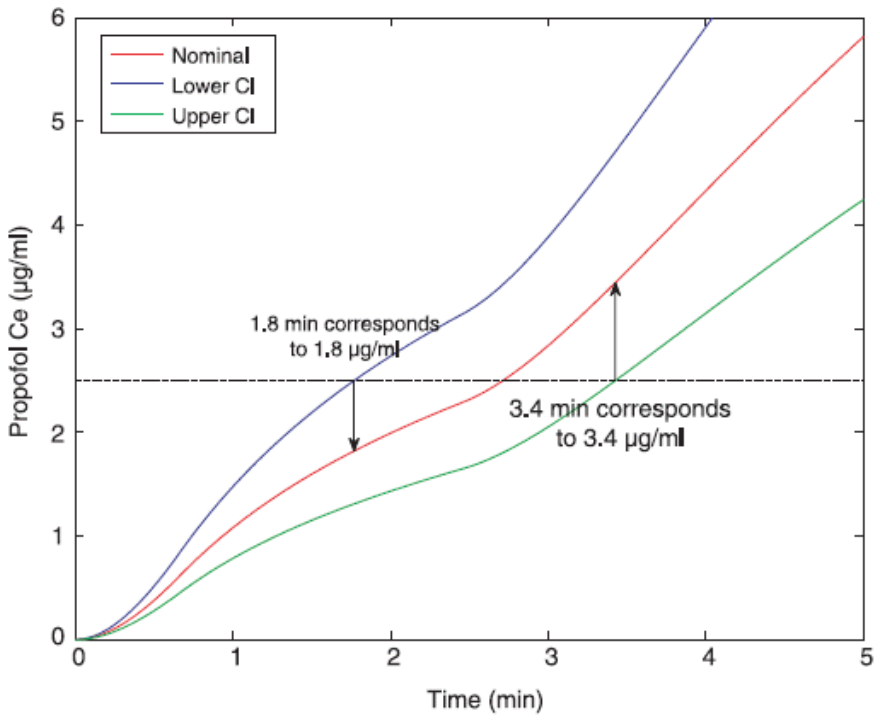
PD+I Controller

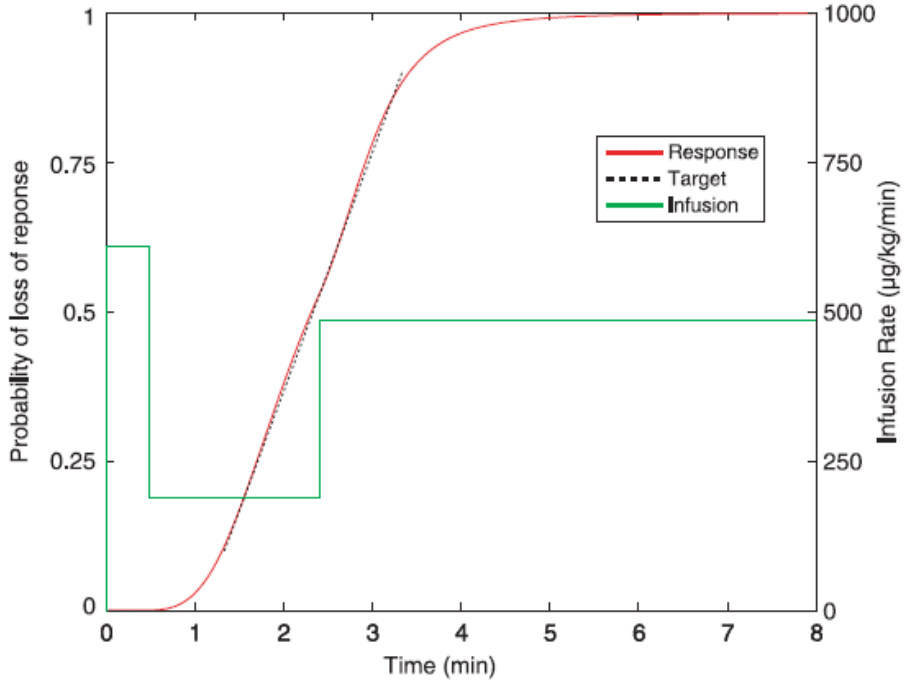
Society for Ambulatory Anesthesiology

Section Editor: Peter S. A. Glass

Safety and Efficacy of Drug-Induced Sleep Endoscopy Using a Probability Ramp Propofol Infusion System in Patients with Severe Obstructive Sleep Apnea

Joshua H. Atkins, MD, PhD,* Jeff E. Mandel, MD, MS,* and Giulia Rosanova, BA†





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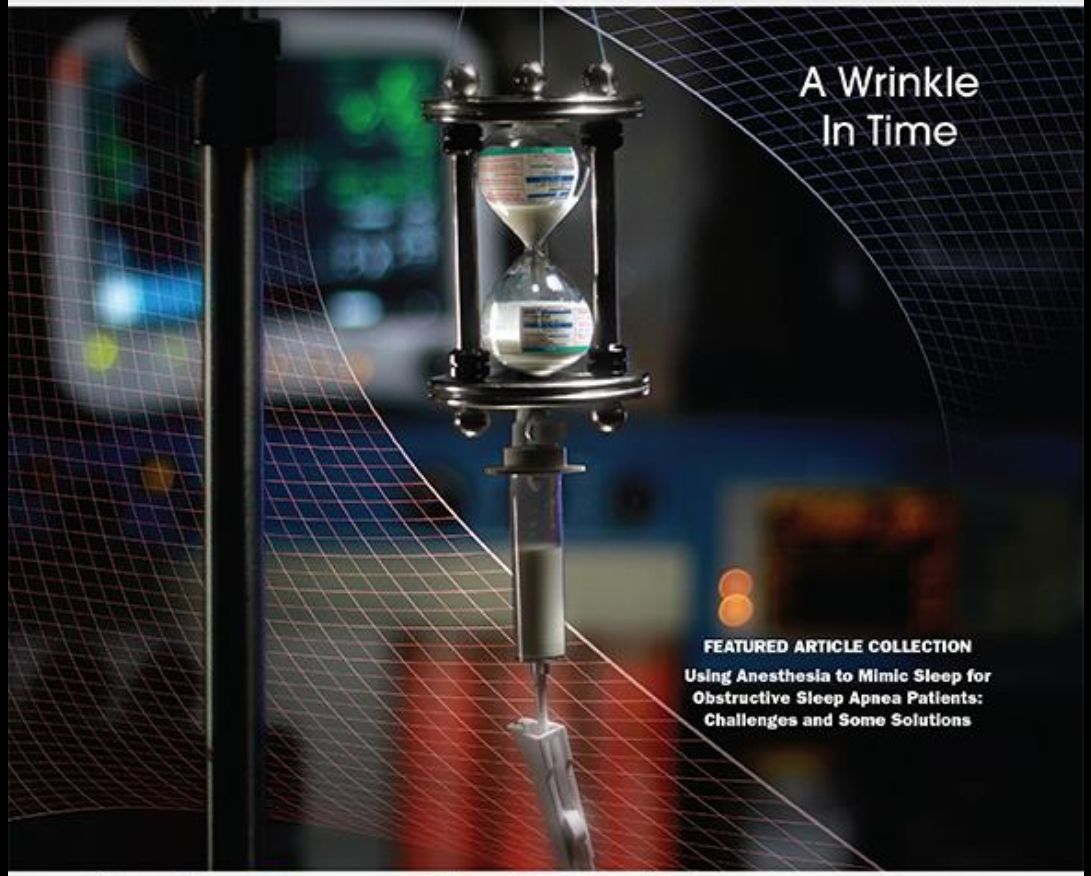
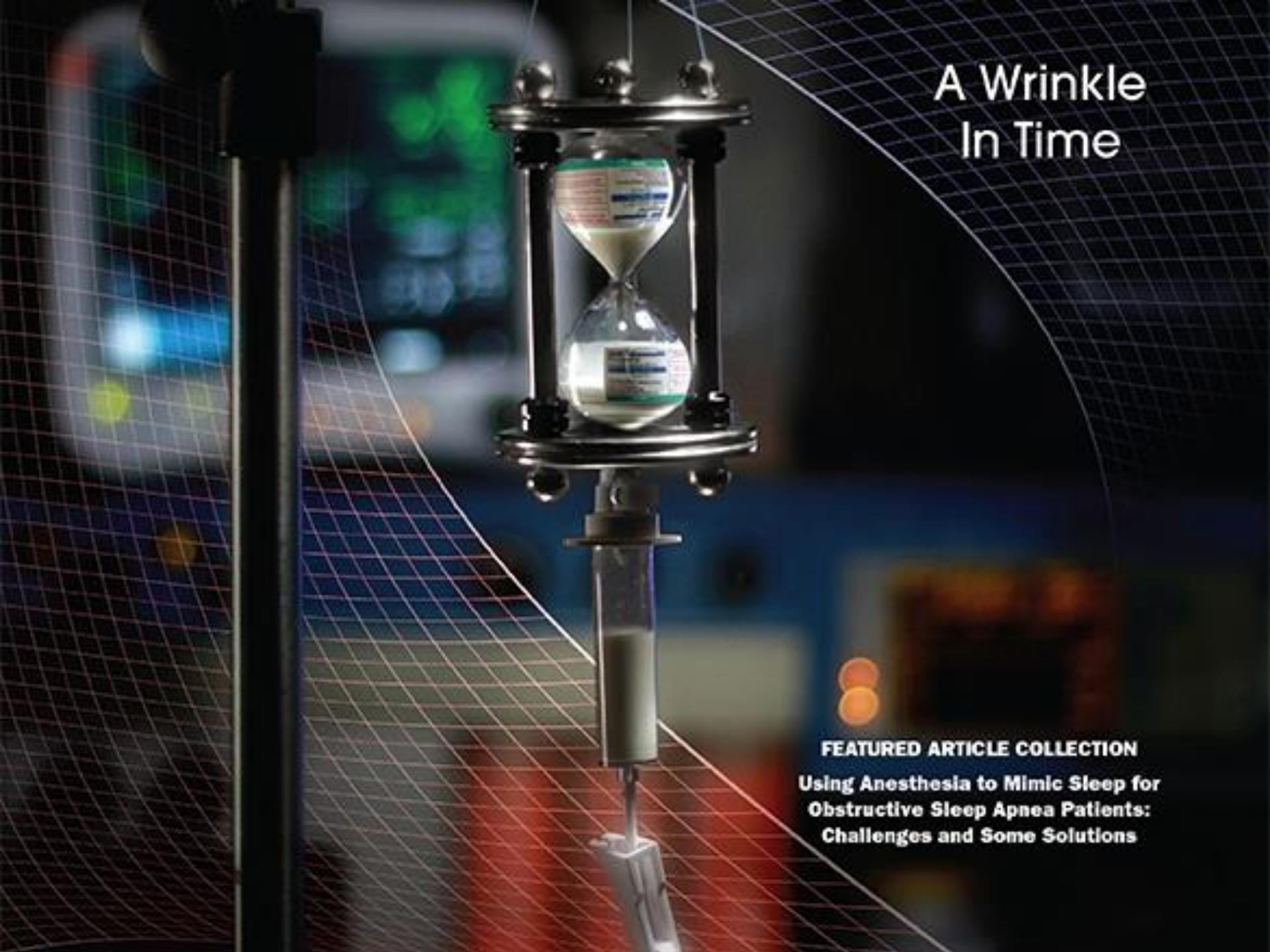


A Wrinkle In Time

FEATURED ARTICLE COLLECTION

Using Anesthesia to Mimic Sleep for Obstructive Sleep Apnea Patients: Challenges and Some Solutions

IARS International Anesthesia Research Society


A Wrinkle
In Time
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Using Anesthesia to Mimic Sleep for
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British Journal of Anaesthesia **110** (6): 1031–9 (2013)
Advance Access publication 20 February 2013 · doi:10.1093/bja/aet001

BJA

QUALITY AND PATIENT SAFETY

Evaluation of a novel closed-loop total intravenous anaesthesia drug delivery system: a randomized controlled trial

T. M. Hemmerling[1*], E. Arbeid[2], M. Wehbe[1], S. Cyr[1], R. Taddei[2] and C. Zaouter[2]

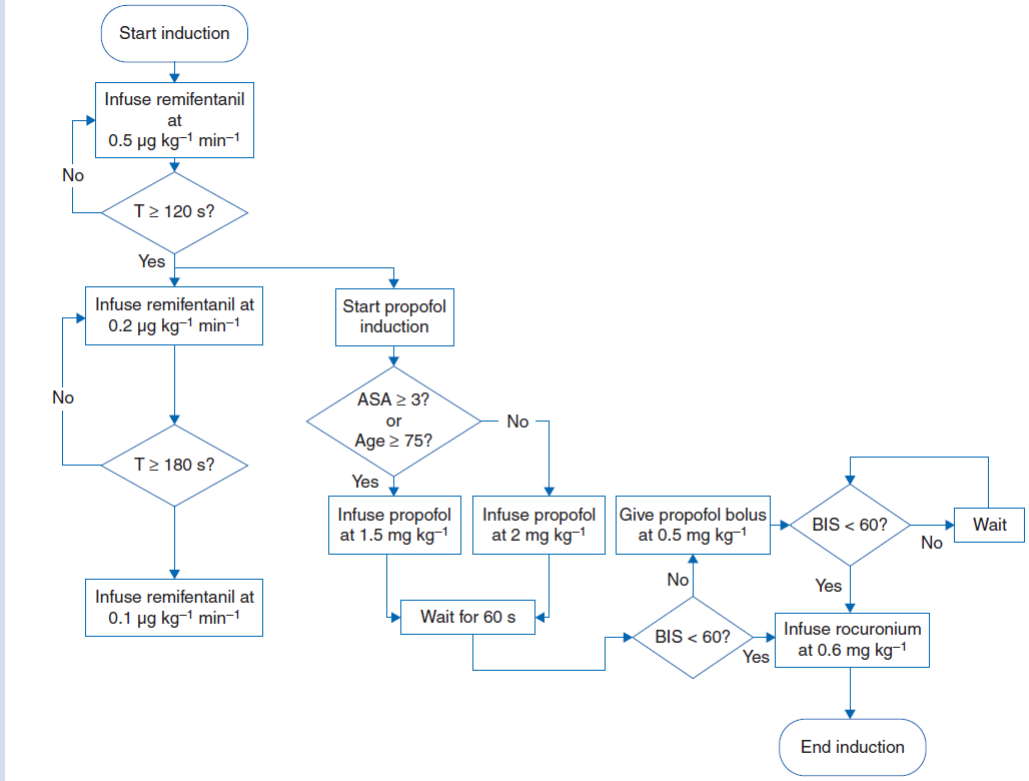

Fig 3 Flow chart showing the induction phase of the McSleepy group.

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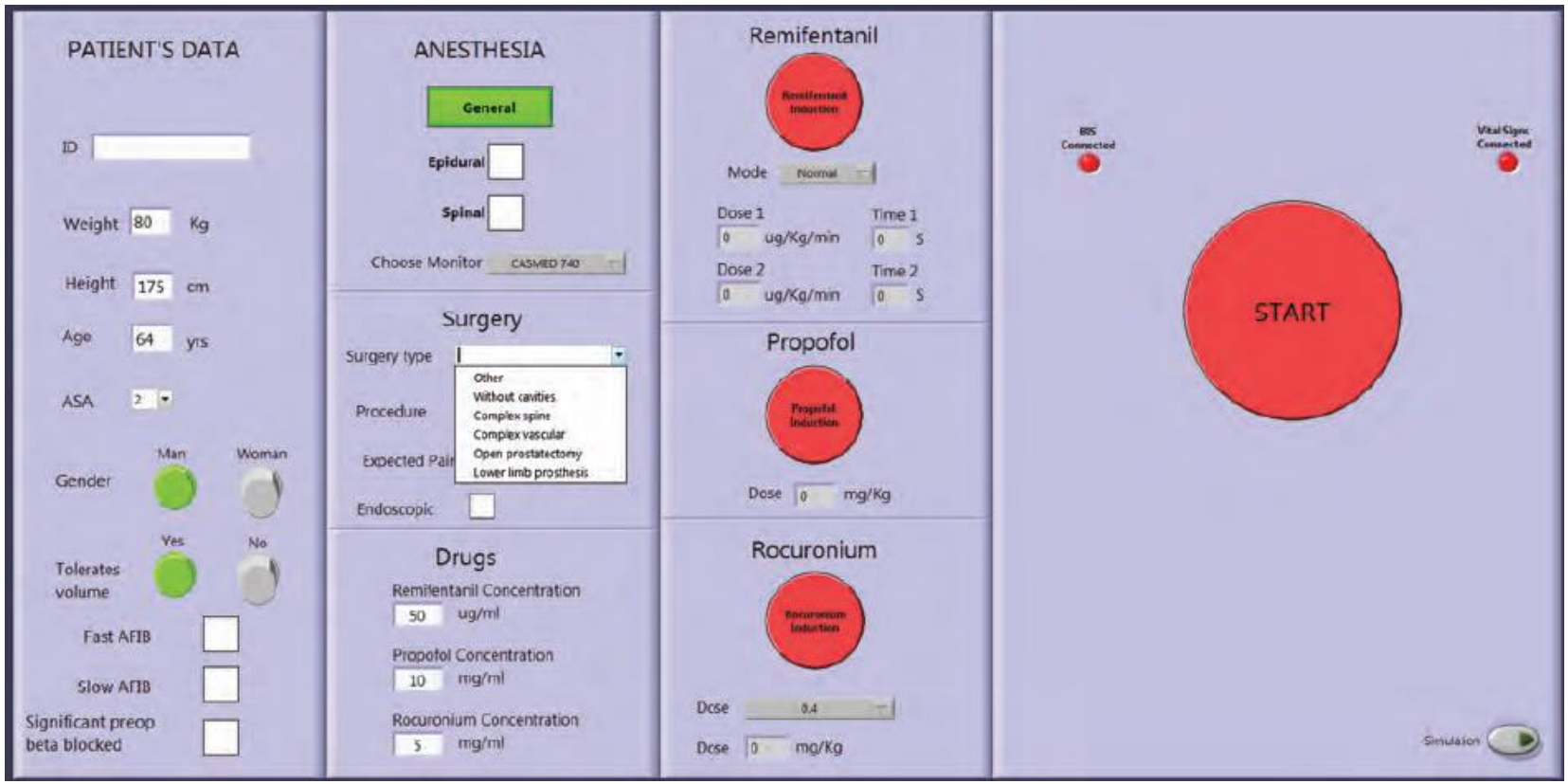

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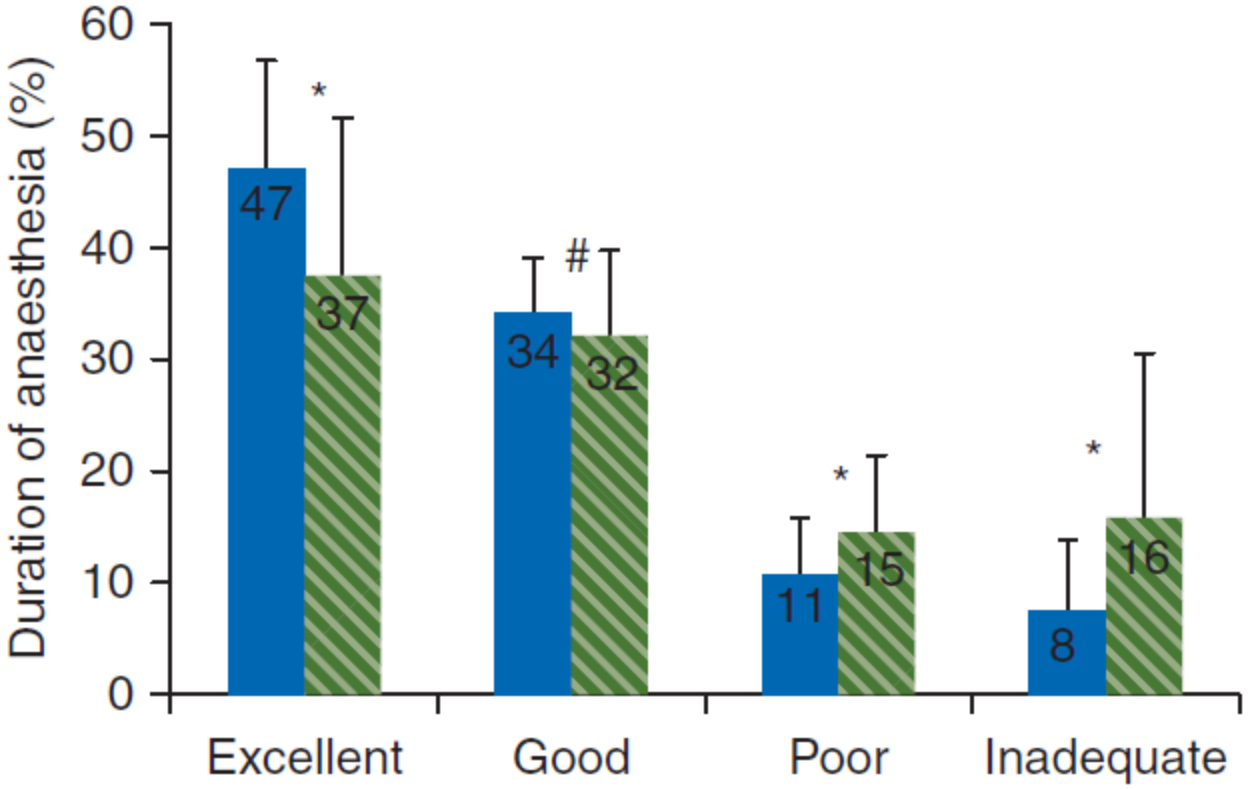

Car Crashes Kill 40,000 in U.S. Every Year

Published February 03, 2005 · WebMD

Imagine a plane full of people crashing, killing everyone on board, every single day. That's how many people die on America's roads daily, says the Insurance Institute for Highway Safety.

"Motor vehicle crashes in the United States result in more than 40,000 deaths per year," says the Institute in the journal Injury Prevention. "That is, on each of the 6,209 consecutive days included in this study, an equivalent of a plane load or more of people died on the roads."

But not all days are alike. Weekends are worse than weekdays, summer and fall months have more deadly crashes than winter or spring months, and holidays top the list for crash deaths.

The Institute studied U.S. Department of Transportation data from 1986-2002. Information covered crashes on public roads resulting in a death within 30 days, including pedestrian deaths.

On average, more than 100 people per day died in car crashes in the U.S. The death toll for a single day can range from 45 to 252 people, say the researchers.

November 1999

INSTITUTE OF MEDICINE

Shaping the Future for Health

TO ERR IS HUMAN:
BUILDING A SAFER HEALTH SYSTEM

Health care in the United States is not as safe as it should be--and can be. At least 44,000 people, and perhaps as many as 98,000 people, die in hospitals each year as a result of medical errors that could have been prevented, according to estimates from two major studies. Even using the lower estimate, preventable medical errors in hospitals exceed attributable deaths to such feared threats as motor-vehicle wrecks, breast cancer, and AIDS.

Best Care at Lower Cost

The Path to Continuously Learning Health Care in America

Mark D. Smith, MD, MBA, *Study Chair*

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

Advising the nation / Improving health

The Vision

New Tools

- Computing Power
- Connectivity
- Improvements in organizational capabilities
- Collaboration between teams of clinicians and with patients

To Err is **HUMAN**

- Computers don't yell, argue, have substance abuse problems, fall asleep, get angry, get hungry, get moody, get cold, flirt, bully, sulk, pee, get sick, get migraines, ignore alarms, forget why they are there.
- We have a responsibility to use computing technology wherever we can deploy it to reduce human error.

Barriers to Innovation in Anesthetic Drug Delivery

Primary candidates for innovation are generic

Rocuronium Remifentanil Propofol Dexmedetomidine

If innovation in anesthesia drug delivery requires changes in the product label,

WE WILL NEVER SEE INNOVATION IN ANESTHETIC DRUG DELIVERY

What about SEDASYS?

$500,000,000

Initiation of MAC Sedation: For initiation of MAC sedation, either an infusion or a slow injection method may be utilized while closely monitoring cardiorespiratory function. With the infusion method, sedation may be initiated by infusing DIPRIVAN Injectable Emulsion at **100 to 150 µg/kg/min (6 to 9 mg/kg/h) for a period of 3 to 5 minutes** and titrating to the desired clinical effect while closely monitoring respiratory function. With the slow injection method for initiation, patients will require approximately 0.5 mg/kg administered over 3 to 5 minutes and titrated to clinical responses. When DIPRIVAN Injectable Emulsion is administered slowly over 3 to 5 minutes, most patients will be adequately sedated, and the peak drug effect can be achieved while minimizing undesirable cardiorespiratory effects occurring at high plasma levels.

In the elderly, debilitated, or ASA III/IV patients, rapid (single or repeated) bolus dose administration should not be used for MAC sedation. (See WARNINGS .) The rate of **administration should be over 3-5 minutes** and the dosage of DIPRIVAN Injectable Emulsion should be reduced to **approximately 80%** of the usual adult dosage in these patients according to their condition, responses, and changes in vital signs. (See DOSAGE AND ADMINISTRATION .)

Maintenance of MAC Sedation: For maintenance of sedation, a variable rate infusion method is preferable over an intermittent bolus dose method. With the variable rate infusion method, patients will generally require maintenance rates of **25 to 75 µg/kg/min** (1.5 to 4.5 mg/kg/h) **during the first 10 to 15 minutes** of sedation maintenance. Infusion rates should subsequently be **decreased** over time to **25 to 50 µg/kg/min** and adjusted to clinical responses. In titrating to clinical effect, allow approximately **2 minutes for onset** of peak drug effect.

Sedasys is NOT groundbreaking

- The $500,000,000 price tag can never be justified for an anesthetic drug delivery system.
- Inflexible adherence to the drug package insert will kill innovation.
  - Sedasys was lucky that rigid adherence to the propofol label actually worked.

Overcoming Barriers

- TCI devices give
  - approved drugs
  - by approved routes
  - for approved indications
  - at doses that conform to the package insert
- *There should be minimal regulatory burden for TCI devices since the drug, route, indication, and doses are approved.*

Redefine “dose”

- If the “dose” of drug administered by new technology is “substantially equivalent to the dose stated in the package insert”, then the device conforms to the label.
- *Just a clarification of the phrase “mutually conforming dose.”*
- Permits infusions to replace boluses
- Permits rapid changes and titrations that only computers can accomplish

Innovation Will Eliminate the Need for Inhalation Anesthesia

The statement is **false,**
until there is a path to bringing innovation in anesthetic drug delivery to the United States

Regulatory Considerations and Closed Loop Anesthetic Delivery Systems

Bahram Parvinian

Why will this time be different?